HELICOBACTER PYLORI GASTRITIS
UPDATED SYDNEY CLASSIFICATION APPLIED
IN OUR MATERIAL

Manxhuka-Kerliu Suzana,1 Telaku Skender,2 Devoll-Disha Emine,3
Ahmetaj Halil,4 Sahatçiu-Meka Vjolca,3 Kerliu Agron,4 Loxha Sadushe,6
Shahini Labinot,6 Gashi Goneta,6 Podrimaj Arijeta6

1Institute of Pathology, Faculty of Medicine (FM), University of Prishtina (UP), Kosovo
2The Clinic of Internal Medicine; Gastroenterology section, FM, UP
3Department of Radiology, FM, UP
4Institute of Pathophysiology, FM, UP
5Physiatric Clinic, FM, UP
6Institute of Pathology, FM, UP, Kosovo

Abstract: Background. Hp inhabits the stomach of more than 50% of humans and is the most frequent cause of chronic gastritis worldwide. The purpose of this research has been to present the importance of combining topographical, morphological and etiological information of diagnostic evaluation on grading gastritis in our material according to the Updated Sydney Classification, as well as to represent the frequency and the evaluation of Hp gastritis after eradication in order to prevent the development of gastric cancer.

Materials and Methods. 154 cases of gastric mucosa (endoscopic biopsies) which were fixed in buffered neutral formalin and embedded in paraffin were invesigated. Tissue sections (5μm thick) were cut and stained with H&E, May Grünwald Giemsa and Silver stain. The biopsy cases were analysed in an attempt to assess the major histopathological features of gastritis. The histopathological major variables were graded on a scale of 3 (mild, moderate and severe).

Results. There were 36 (23.37%) cases positive for Hp (22.2%, 72.2%, 5.5%). Atrophy was positive in 23 (14.93%) cases with the scale (47.8%; 47.8%; 4.34%). Dysplasia was positive in 13 (8.44%) cases with the scale (84.6%; 7.6%; 7.6%). Intestinal metaplasia was positive in 25 (16.2%) with the scale (76%; 20%; 4%). There were 6 (3.8%) cases of MZL, which were treated appropriately.
Conclusions. Our data indicate the importance of early eradication of Helicobacter pylori in order to prevent the eventual development of gastric cancer. These findings should influence the treatment of gastric cancers.

Key words: Updated Sydney System of Classification, Hp gastritis, morphology.

Introduction

Helicobacter gastritis is a primary infection of the stomach and is the most frequent cause of chronic gastritis. H pylori are gram-negative rods that have the ability to colonize and infect the stomach. The bacteria survive within the mucous layer that covers the gastric surface epithelium and the upper portions of the gastric foveolae. The infection is usually acquired in childhood [29]. Once the organism has been acquired, has passed through the mucous layer, and has become established at the luminal surface of the stomach, an intense inflammatory response of the underlying tissue develops.

Warren & Marshall discovered that Helicobacter pylori (Hp) are a causative agent of gastritis. Hp inhabits the stomach of more than 50% of humans and is the most frequent cause of chronic gastritis worldwide [1, 2, 3, 4, 19, 29, 30].

The Sydney system is a novel classification and grading of gastritis that was devised by a group of experts at the 9th World Congress of Gastroenterology in Sydney, Australia in 1990. Experts emphasized the importance of combining topographical, morphological and etiological information for the diagnostic evaluation of gastritis. In 1994 in Houston, Texas, experts devised the new updated Sydney system [1, 2, 3, 4].

In general, gastritis is classified into acute and chronic gastritis. Chronic gastritis is divided into nonatrophic chronic gastritis, usually caused by Hp infection, and atrophic gastritis composed of autoimmune and multifocal atrophic gastritis caused by Hp or dietary factors, as well as special forms of gastritis composed of reactive (chemical, reflux), radiation, lymphocytic, non-infectious granulomatous, eosinophylic and other infectious gastritides [8, 18, 23, 32].

However, the presence of Hp in a biopsy specimen does not mean that it is the sole aetiologic agent. In some cases there are multiple aetiologic agents [11, 12, 14, 15].

The presence of Hp is associated with tissue damage and histologic finding of chronic gastritis. The sites of the biopsy are important for an accurate diagnosis. In the updated Sydney system, five biopsy sites were recommended, including the incisura [17].
The Updated Sydney System proposed the use of visual scales as a reference standard for grading: the density of Hp infection; acute and chronic inflammation; IM (16) and atrophy [7, 20, 21].

*Hp*-identification

*Hp*-associated chronic gastritis progresses with the following 2 main topographic patterns that have different clinical consequences:

- Antral predominant gastritis is characterized by inflammation and is mostly limited to the antrum. Individuals with peptic ulcers usually demonstrate this pattern of gastritis.

- Multifocal atrophic gastritis is characterized by involvement of the corpus and gastric antrum with progressive development of gastric atrophy (loss of the gastric glands) and partial replacement of the gastric glands by an intestinal-type epithelium (intestinal metaplasia). Individuals who develop gastric carcinoma and gastric ulcers usually demonstrate this pattern of gastritis [4, 5, 6, 7, 23, 31, 33, 36].

*Hp* are found in the mucin covering the surface epithelium and within the foveolae, therefore they could be detected by H&E stain when they are numerous but, if they are rare, there are many staining methods for *Hp* such as: Warthin-Starry; Cresyl-violet, Gimminez, Alcian yellow-toluidine blu-Leung, Genta stain, Giemsa, May Grünwald Giemsa. Samples for detecting *Hp* should be taken before treatment [33, 36, 37].

*Hp*-pathogenesis

*Hp*-pathogenesis is not yet clear. *Hp* is genetically heterogeneous and all strains may not play the same role in the development of malignancy. People infected with *H pylori* strains that secrete the vacuolating toxin A (vacA) are more likely to develop peptic ulcers than people infected with strains that do not secrete this toxin. Another set of virulence factors is encoded by the *H pylori* pathogenicity island (PAI). The PAI contains the sequence for several genes and encodes the CAGA gene. Strains that produce CagA protein (CagA+) are associated with a greater risk of development of gastric carcinoma and peptic ulcer. However, infection with CagA- strains also predisposes the person to these diseases. Strains containing a group of genes named cag pathogenicity islands induce a greater degree of inflammation than strains lacking these genes. The mechanism involves epithelial production of interleukin 8 via nuclear factor kappa B pathway. CagA+ strains cause severe inflammation response in association with peptic ulcer, atrophic gastritis, IM-cancer. [9, 13, 25, 40, 41, 42, 44]

*First Hp colonization*

*Hp* in its first colonization causes an acute superficial gastritis:
– Neutrophil infiltration between surface and foveolar epithelial cells and within gastric pits,
– Surface epithelium shows degenerative changes with loss of mucin and increased exfoliation,
– First affected antral mucosa – later corpus mucosa,
– Lymphoplasmacytic infiltration increases after 11–14 days,
– Lamina propria is edematous.

**Chronic Hp infection**

Mononuclear infiltration:
– Foveolar predilection,
– Neutrophil active infiltration in the neck region (proliferative zone of gastric mucosa), intersticium and foveolar epithelium,
– Lymphoid aggregate with germinal centres,
– Chronic Hp gastritis – antral predominance.

Chronic Hp gastritis can be multifocal with multifocal atrophy and IM which where important long-term sequels.

After eradication of Hp:
– Neutrophils disappear after 6–8 weeks,
– Chronic infiltration persists longer – antral region [43].

An important question is whether *H pylori* eradication in a patient with atrophic gastritis reduces the risk of gastric cancer development. Limited data are available, but a prospective study in a Japanese population reported that *H pylori* eradication in patients with endoscopically resected early gastric cancer resulted in the decreased appearance of new early cancers, while intestinal-type gastric cancers developed in the control group without *H pylori* eradication [10]. These findings support an intervention approach with eradication of *H pylori* if the organisms are detected in patients with atrophic gastritis; the goal is to prevent the development of gastric cancer [7, 9, 24, 26, 35, 39].

**Diseases associated with Hp gastritis**

*Helicobacter pylori* cause chronic gastritis, peptic ulcer, gastric cancer and mucosa-associated lymphoid tissue (MALT) lymphoma. [38] The diversity of clinical outcomes associated with *H. pylori* infection is probably a result of the interactions among host, environmental, and bacterial virulence factors [28].

– Hyperplastic polyps,
– Lymphocytic gastritis, [8]
– Anaemia,
Helicobacter pylori gastritis...

– Peptic ulcer disease, [22, 41]
– Duodenitis,
– IM,
– The most important long-term sequel of chronic Hp Gastritis with IM is a gastric carcinoma.

Gastric carcinogenesis
Helicobacter pylori interact with gastric epithelial cells, activating signalling pathways important for carcinogenesis.
E-cadherine methylation is an early event initiated by Hp infection.
Hp causes the hyperproliferation of the gastric epithelium, a state that increases the risk of mutation collection and neoplastic transformation.
Infiltrating neutrophils of Hp gastritis release various inflammatory mediators and toxic oxidants functioning as mutagens. IM is regarded as a condition that predisposes to carcinoma.

Gene alterations (Microsatellite instability, loss of heterozygosity, p53 mutations) found in carcinoma have been reported in IM which explains its malignant potential [9, 27, 34, 44].

The aim of the research
The purpose of this research is the evaluation of gastric biopsy material of the Pathology Institute, University of Prishtina in order to:
– present the importance of combining topographical, morphological and etiological information for the diagnostic evaluation of Hp-gastritis according to the Updated Sydney Classification on grading of Hp gastritis in our material;
– present the frequency of Hp gastritis and other consequent morphological changes such as metaplasia, dysplasia and gastric cancer (lymphoma, carcinoma);
– present the importance of eradication of Hp gastritis, in order to prevent the development of gastric cancer.

Material and methods
154 cases of gastric mucosa (endoscopic biopsies from the antrum and corpus) which were fixed in buffered neutral formalin and embedded in paraffin were investigated. Tissue sections (5μm thick) were cut and stained with haematoxylin and eosin (H&E) stain, May Grünwald Giemsa and Silver stain. Two to five gastric antral biopsy specimens were taken from the greater and
lesser curvature, within 2 cm of the fundamental pyloric border, before and after Hp eradication treatment. However, for the accurate diagnosis of gastric atrophy, biopsy specimens were taken from the mid antrum and the mid body of the lesser and greater curvature.

The biopsy cases were analysed in an attempt to assess the major histopathological features of gastritis. Semi-quantitative method of scoring according to the Updated Sydney Classification System was undertaken. The histopathological variables (Hp density, neutrophil and mononuclear infiltration, atrophy, intestinal metaplasia and dysplasia were graded on a scale of 3 (mild, moderate and severe). Minor histopathological features were not graded, but simply assessed in case of their presence or absence. H. pylori colonization was assessed and graded after careful search for focal or complete involvement of the gastric surface.

The degree of inflammatory activity was investigated for involvement according to the density of neutrophils in gastric mucosal crypts, from one to all crypts.

Superficial epithelial damage was scored depending on the degeneration process of the epithelial cells with disorientation of the epithelium lining. In addition, the degree of mononuclear infiltration was investigated.

The degree of intestinal metaplasia was assessed and graded according to the amount of glandular tissue replaced by intestinal type epithelium.

Mucosal atrophy was defined as a loss of specialized gastric glands in mucosa, partly replaced by intestinal metaplastic epithelium. It was characterized by architectural changes manifested by variation in the volume and irregularity in the shape, branching, and spacing of the glands. Other factors such as lamina propria, including myofibroblasts and inflammatory cells, might react with the gland to produce structural alterations, which may lead to architectural, metaplastic, proliferative and functional changes.

Dysplasia was also assessed as an important factor in the histological sequence leading to gastric cancer.

Statistical analyses of obtained data were performed.

Results

154 cases of gastric mucosa (endoscopic biopsies from the antrum and corpus) were investigated. 103 (66.88%) cases were positive for major variables while 51 (33.11%) cases were negative, unsuitable for histological evaluation according to the Sydney System. During this research, semi-quantitative methods of scoring according to the Updated Sydney Classification System were
undertaken. Hp density in our material was greater in the antrum than in the corpus. The density of Hp colonization was graded as mild, moderate and severe. During our research we found 22.2% mild colonization, and 72.2% moderate and 5.5% severe Hp colonization out of a total 23.37% of cases with Hp infection. P < 0.01 (Table 1, Fig. 1).

Table 1 – Табела 1

<table>
<thead>
<tr>
<th>Inflammation</th>
<th>MILD +</th>
<th>MODERATE ++</th>
<th>SEVERE +++</th>
<th>TOTAL</th>
<th>Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total cases</td>
<td>73</td>
<td>47.4</td>
<td>63</td>
<td>40.9</td>
<td>18</td>
</tr>
<tr>
<td>Active</td>
<td>55</td>
<td>35.7</td>
<td>50</td>
<td>32.5</td>
<td>8</td>
</tr>
<tr>
<td>Chronic-no activity</td>
<td>18</td>
<td>11.7</td>
<td>13</td>
<td>8.4</td>
<td>10</td>
</tr>
<tr>
<td>Atrophy</td>
<td>11</td>
<td>47.8</td>
<td>11</td>
<td>47.8</td>
<td>1</td>
</tr>
<tr>
<td>IM</td>
<td>19</td>
<td>76.0</td>
<td>5</td>
<td>20.0</td>
<td>1</td>
</tr>
<tr>
<td>HP</td>
<td>8</td>
<td>22.2</td>
<td>26</td>
<td>72.2</td>
<td>2</td>
</tr>
<tr>
<td>Dysplasia</td>
<td>11</td>
<td>84.6</td>
<td>1</td>
<td>7.6</td>
<td>1</td>
</tr>
<tr>
<td>MZL</td>
<td>0</td>
<td>0.0</td>
<td>0</td>
<td>0.0</td>
<td>0</td>
</tr>
</tbody>
</table>

The degree of inflammatory activity was assessed and graded as follows: 35% mild; 32% moderate and 5.5% severe out of a total 73.5% cases in an active phase of Hp gastritis, P < 0,0001. As far as chronic inflammation is concerned, there were 11.5% mild, 8.5% moderate and 6.5% severe out of the total of 26.5% of Hp gastritis with chronic infiltration. P > 0,05 (Table 1, Fig. 1, 2).

Hp-associated gastritis was the most common form of chronic gastritis, while intestinal metaplasia and atrophy were also higher in the antrum. Intestinal metaplasia was graded in 76% of cases as mild, in 20% as moderate and in 5.5% as severe out of the total of 16.23% of cases with intestinal metaplasia, P < 0.01 (Table 1, Fig. 3, 4).

Приложение. Одд. биол. мед. наука. ХХХ/1 (2009), 45–60
Hp positive patients attended first and second follow-up endoscopy visits. After the failure of the first line of treatment with omeprazole, especially in patients with severe damage to the gastric tissue, they were treated with triple treatment composed of one dose of tineaosal, doxycycline for two weeks and bismuth subcitrate for four weeks.

After this treatment the eradication of Hp was accomplished. Neutrophils disappeared within 6–8 weeks, but chronic inflammation as well as other major Hp features persisted longer. A characteristic feature of the chronic gastritis induced by *Helicobacter pylori* (Hp) is the presence of mucosa-associated lymphoid tissue (MALT), which consists of lymphoid aggregates and organized follicles. MALT is not normally found in the stomach mucosa and disappears after eradication of the infection, suggesting that Hp is the causative agent (Table 1, Graph 1).
We found MALT lesion in 15.5% of 26.5% cases with no active inflammation, whereas MZL was found in 3.8% of the total of 154 patients examined in this research. Cases with MZL were treated appropriately (Table 1, Fig. 5, 6, 7, 8).

Graph. 1 – Hp colonisation
Графикон 1 – Нр колонизација

Figure 5 – Gastritis MALT and infection with Helicobacter pylori (H&E stain)
Слика 5 – Гастритична MALT и инфекција со Helicobacter pilory (боewe со H&E)

Figure 6 – Gastritis MALT and infection with Helicobacter pylori (May Grünwald Giemsa stain)
Слика 6 – Гастритична MALT и инфекција со Helicobakter pilori (боewe со May Grünwald Giemsa)

Figure 7 – Gastritis MALT lymphoma (H&E stain – low magnification)
Слика 7 – Гастритичен MALT лимфом (боewe со H&E – со мало зголемување)

Figure 8 – Gastritis MALT lymphoma (H&E stain – high magnification)
Слика 8 – Гастритичен MALT лимфом (боewe со H&E – со големо зголемување)
The gastric atrophy was characterised by changes in the epithelium and stroma of body-type and antral-type gastric mucosa, with partial or complete loss of the glandular epithelium which may lead to architectural, metaplastic, proliferative and functional changes. While assessing and grading the atrophy, criteria such as: the presence of intestinal metaplasia, the number of coils, and disturbance of pit numbers in relation to those of glandular structure and the presence of fibrosis were used.

Atrophic gastritis was observed as a result of long standing Hp infection. The clinical importance of gastric atrophy was that it significantly increased the risk of the development of gastric carcinoma. The prevalence and density of Hp infection decreased in proportion to advances in the cancer stage and the mucosal atrophy.

The degree of atrophy was assessed and graded in mild and moderate in 47.8% each, and severe in 4.34% of a total of 14.93% cases with atrophic changes, P < 0.05. High-grade gastric atrophy, in our material, was observed in 4.34%, combined with high grade-IM in 4% and associated with high grade-gastric dysplasia in 7.6%. Dysplastic changes were found in 8.44% of our cases with Hp gastritis, which were also each graded as mild in 84.6%, moderate and severe in 7.6%, P < 0.01 (Table 1, Graph. 1, Figs. 9, 10).

Discussion & conclusion

Population Helicobacter pylori screening and treatment has the potential of dramatically reducing global gastric cancer mortality [30].

Our data show a higher percentage of major histopathological features such as atrophia, IM and dysplasia in cases of Hp gastritis. Since the presence
of *H. pylori* increases the chances of developing adenocarcinoma and MALT lymphoma, early detection and eradication of Hp gastritis is of great importance for our patients in order to prevent the development of precancerous changes and gastric cancer.

In terms of treatment, eradication of *H. pylori* helps treat MALT lymphomas. Many studies show that MALT lymphomas regress with the eradication of *H. pylori*. That happened in 6 of our cases of Malt lymphomas. However, adenocarcinoma is not known to regress with the eradication of *H. pylori*. Therefore, eradication of *H. pylori* is only effective prior to the development of adenocarcinoma. The similarity of the annual recurrence rates during the first year after eradication and the annual recurrence rates in the second year after successful eradication in developing countries supports reinfection as the main cause in the second period. Therefore, a different approach to the follow-up of *H. pylori* eradication may be required in developed and developing countries [30, 37].

The debate on *H. pylori* as a factor in gastric cancer is ongoing. Currently eradication of *H. pylori* in high-risk patients is required to provide adequate treatment and prevention of gastric cancer.

The sites of the biopsy are important for an accurate diagnosis of gastric atrophy. According to the Updated Sydney Classification System, five biopsy sites were recommended, including the incisura. Four biopsies should be taken from the mid antrum and mid body of the lesser curvature and the mid antrum and mid body of the greater curvature.

Thus the Sydney system-based grading scale applied in our material provided an objective histological evaluation of Hp gastritis and was of great value in estimating treatment efficacy.

**Acknowledgments**

This study was supported by the Institute of Anatomic Pathology, Pathophysiology, Histology, Internal Medicine – Gastroenterology Department, University of Prishtina.

**REFERENCES**


РЕЗИМЕ

HELICOBACTER PYLORI ГАСТРИТИС КЛАСИФИКАЦИЈА ПО НОВИОТ SYDNEY СИСТЕМ АПЛИЦИРАН НА НАШИОТ МАТЕРИЈАЛ

Мацкука-Керлиу Сузана,1 Телаку Скендер,2 Деволлз-Дисха Емине,3 Ахмета Халил,4 Сахатцн-Мека Вјолца,5 Керлиу Агрон,4 Лоћка Садусе,6 Сахини Лабинот,6 Гасхи Гонета,4 Подрииај Аријета6

1 Институт за патологиа, Медиски факултет (МФ), Прирски универзитет (ПУ), Косово
2 Клиника за интерна медицина; Гастроентерологиа, МФ, ПУ, Косово
3 Клиника за радиологиа, МФ, ПУ, Косово
4 Институт за патофизиологиа, МФ, ПУ, Косово
5 Клиника за физиатрија, МФ, ПУ, Косово
6 Институт за патологиа, МФ, ПУ, Косово

Вовед. Hp се појавува повеќе од 50% во желудникот кај луѓето и е еден од најчестите причинители на хроничниот гастритис во целот свет. Целта на ова истражување беше да се презентира важноста на комбинацијата на топографски, морфолошки и етилошки информации на дијагностичката евалуација и степенувањето на гастритисот во нашиот материјал според новата Sydney класификација. Како и презентирањето на фреквентијата, евалуацијата на Hp гастритисот по лечењето, како превенција за развивање на гастритичниот рак.

Материјал и методи. Беше испитани 154 случаи на гастритична мукоза (ендоскопски биопси), кои се фиксирани во неутрален буферен формалин и калпуриран во парафин. Секциите на ткивата (дебелина 5 μм) беше пресечени и боени со H&E, May Grünwald Giemsa и Silver. Биопсите се анализираани со цел да се проценат главните хистопатолошки слики на гастритисот. Малите хистопатолошки промени беше степенувани во 3 степени (лесно, средно и тешко).

Резултати. Пронајдени се 36 (23,37%) случаи на Hp позитивни со степен (22,2%, 72,2%, 5,5%).

Атрофитата беше позитивна во 23 (14,93%) случаи со степен (47,8%; 47,8%; 4,34%).

Дисплазијата беше позитивна во 13 (8,44%) случаи со степен (84,6%; 7,6%; 7,6%).

Интекстиналната метаплазија беше позитивна во 25 (16,2%) случаи со степен (76%, 20%, 4%). Во 6 (3,8%) случаи е најдено МЗЛ, кој е адекватно лечен.
Заклучок. Нашите податоци ја покажуваат важноста на раната ерадикација на Helicobacter pilory, како превенција за евентуално развивање на гастритичниот рак. Овие констатации треба да укажат на третманот на гастритичниот рак.

Ключни зборови: класификација според новиот Sydney Sistem, Nr гастритис, морфологија.

Corresponding Author:
Prof. Dr Suzana Manxhuka-Kerliu,
Pathology Institute, Faculty of Medicine,
University of Prishtina,
Mother Theresa str.
Prishtina, 10 000, Kosovo.
Tel: +377 44 153 400
E-mail:suzanakerliu@uni-pr.edu