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Review

From Sidney to OLGA: an overview of atrophic gastritis

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Summary. Chronic gastritis is a long-lasting disease that can lead to a loss of appropriate gastric glands. Gastritis, as term, apply to an inflammation of the stomach, histologically proven, sometimes with structural mucosal changes. Worldwide Helicobacter pylori's infection play a pivotal role as the main etiological effector of chronic active gastritis. H. p. is a bacterium with a selective tropism for the gastric mucosa, able to survive in a hostile environment for colonization of organisms other than itself, able to develop strategies for survival and for avoidance of the defence mechanisms, causing inflammatory changes, that vary from asymptomatic mild gastritis to more severe injury such as peptic ulcer as well as premalignant lesions and malignant tumours. The pattern and distribution of gastritis strongly correlate with these sequelae and chronic atrophic gastritis with intestinal metaplasia is now assessed as a precancerous lesion with definite risk of evolution towards intraepithelial lesions of both low and high grade, as expected in the model of the Correa's cascade. In fact, the leading complication of chronic gastritis remains its close correlation with gastric cancer being biologically linked to H. pylori infection, nowadays known as a class I carcinogen. Gastric carcinogenesis is due to environmental factors, as well as to bacterial strain, host responses and gastric mucosal microbiome dysbiosis. Since, individual patients show different gastric cancer risk, it is mandatory to identify patients at risk of developing gastric cancer to offer a targeted search for lesions with a more rapid development of neoplasm liable, in an early phase, to a less destructive treatment. OLGA staging system is the most reliable and powerful system that allow the recognition of patient with a higher risk of developing gastric cancer. (www.actabiomedica.it)

Key words: chronic atrophic gastritis, OLGA, Sidney system, OLGIM

Introduction

Although fully recognized in 1984 (1), Helicobacter pylori (H. p.) a spiral shaped, microaerophilic, Gram-negative bacterium probably present in humans for millenia (2), has developed a selective tropism for the gastric mucosa, causing inflammatory changes, that vary from asymptomatic mild gastritis to peptic ulcer, as well as premalignant lesions and malignant tumours, including gastric lymphoma and epithelial gastric neoplasia. H. p. is responsible for a long-standing infection with a slow course, one of the most common chronic infection in humans at the present time (2).

Worldwide, the epidemiology of H. pylori infection, which affects approximately 50% of the world's population, overlaps that of gastritis (3)

A gastritis is an inflammation of the gastric mucosa, histologically proven (4), even when patients have no symptoms and irrespective of complications as stated in the Kyoto consensus report (5), H. pylori being the most frequent causative agent which ultimately interfere with acid and pepsin secretion,

disrupting a unique acid environment that requires functional gastric surface mucus barrier, bicarbonate buffering and epithelial integrity for its functions, making it vulnerable to gastric secretions. In most cases the HP infection is not clinically manifested. Different characteristics of virulence of the infecting strain, such as initial bacterial load, production of toxins (cagA and vacA strains are associated with ulcers and gastric cancer), adhesins, host response such as type and expression of HLA gastric epithelium response to IgA, IgM and IgG immunoglobulin, release of prostaglandins and leukotrienes, mass of the parietal cells and acid secretion, duodenogastric reflux, vascularization of the gastric mucosa and the presence of environmental cofactors such as age at time of infection, dietary factors (salt excess and nitrates, vitamins C and E deficiency), nonsteroidal anti-inflammatory drugs may explain the variability of clinical presentation. For this reason, the diagnostic approach to gastric inflammatory pathology (gastritis) has evolved over time moving on the simple presence of inflammation histologically (biopsies) proved to a pathology that must be approached in a multimodal way where laboratory tests, endoscopy and histology converge to provide a diagnosis not only of specific disease but also providing a picture of the risk of evolution in more serious pathologies.

It is the same informative concept that made it possible to step from the descriptive model of the Sydney System, proposed in 1991 revisited in 1994, known to us as Houston update Sydney System (6), to the current OLGA classification system (7).

The grading systems: The updated Sydney System and OLGA system (Operative Link for Gastritis Assessment system)

The updated Sydney System (6) has been and even now is a widespread used system of reporting that has provided guidelines for pathologists taking into account, in a systematic way, each relevant pathologic feature, such as density of H. pylori, intensity of neutrophilic and mononuclear inflammation, atrophy of the antrum and corpus, and presence/absence of intestinal metaplasia.

In the Sydney System has been recommended that at least five biopsy specimens should be evaluated. This statement has been reassessed in the Kyoto Consensus Report (5) Statement 13 that affirm with a strong grade of recommendation and high level of evidence (Consensus level: 92.1%): accurate histological assessment of gastritis requires biopsy sampling of both antrum and corpus, needing the specimens to be put into separate vials and grouped for each site or lesion or as Italian pathologist do, identified on a squared paper.

The major reason for taking multiple biopsy specimens throughout the gastric mucosa is to assure the correct diagnosis. Most of gastric disease occurs in a disorderly fashion, with an irregular topographic distribution. Therefore, multiple specimens are also necessary to determine disease distribution within the mucosa. The information obtained are useful for the diagnosis, to clarify the etiology and are also important in the differential diagnosis of gastric diseases that may have similar histological features. Multiple specimens from: a) antrum (2) from the lesser and the greater curvature of the antrum, both within 2 to 3 cm from the pylorus; b) antral-body transitional zone (1) from the incisura angularis; and c) corpus (2) from the lesser curvature of the corpus about 4 cm proximal to the angulus and from the middle portion of the greater curvature of the corpus, approximately 8 cm from the cardia should be properly identified and should be submitted in separate containers to the pathology laboratory

In addition, biopsies from any macroscopically lesion should be taken (ulcer, erosion, or depressed area detected etc.). This sampling mode provides the best cost/benefit ratio in terms of diagnostic yield for identifying patients with premalignant lesions and provides a better overview of the severity and distribution of these lesions and the histopathological grading of individual abnormalities—in particular, inflammation, gland loss and metaplasia (5).

Corpus biopsies are particularly valuable for yielding positive results after treatment, especially where proton pump inhibitors have been used. Under these circumstances, organisms may become rare or disappear from the antrum but remain in the oxyntic mucosa, which may also develop cystic dilatations with

hypertrophy of the parietal cells (6). The sample from incisura angularis should be taken into account, given that in such a place can be consistently found metaplastic and dysplastic lesions. It should generally be treated as an additional antral specimen and its scores averaged with the antral ones. OLGA staging system (7) has adopted these indications too.

Sampling orientation is critical for optimal histologic evaluation: fragments shall be deposited with the uneven, rough surface, as such adhers on paper blotting and then into the fixative. This allows proper orientation of the biopsy.

The gastritis characterization is possible whereas each biopsy include the muscularis mucosae, being completely represented the full thickness of the mucosa. Assessments of the degree of atrophy are reliable where the sample should cover at least 15-20 pits. In the Sidney system, in antrum and corpus, the presence of H. p., neutrophilic and mononuclear cells, loss of proper glands of the antrum and corpus, and intestinal metaplasia are recorded and then a numeric or descriptive value are assigned: 0 for absent, 1 for mild, 2 for moderate, and 3 for marked (or severe). This is a basic level represented by a set of elementary lesions (Polymorphonuclear neutrophil activity, Chronic inflammation, Glandular atrophy, Intestinal metaplasia, Other Histological Features (Nongraded Variables) such as Surface epithelial damage, mucous depletion, and erosions, Lymphoid follicles, Foveolar hyperplasia, Pseudopyloric metaplasia, Pancreatic or acinar metaplasia, Endocrine cell hyperplasia), that characterize the morphological pictures allowing to distinguish the topographic types of H. pylori induced chronic gastritis, metaplastic or not, from other subtypes of gastritis that recognize different etiologic agents. But it is only the combination and topographical distribution of the different elementary lesions that returns the overview of gastritis in the individual patient.

Given the considerable variation of intensity within the same biopsy sample in such cases, the observer should attempt to average the different areas and score the specimen accordingly (6). This evaluation attempt led to a variable reproducibility among pathologists.

The degree of inflammation in the antrum and corpus allows to determine whether the inflammation is similar in intensity (i.e., pangastritis) or more severe in either the antrum (antrum-predominant gastritis) or the corpus (corpus-predominant gastritis). Most cases show diffuse chronic inflammation, but a small proportion will show a two-grade difference between the antrum and corpus or vice versa. These cases should be distinguished as antral predominant or corpus predominant, respectively Gastritis staging, combined with H pylori status, provided clinically relevant information on the overall status of the gastric mucosa with implications for prognosis, therapy and management The last step in the Sydney classification is to decide whether focal atrophy or diffuse atrophy is present (metaplastic or nonmetaplastic). With regard to this last topic, the interobserver agreement among pathologists had revisited the spectrum of gastric atrophy and intestinal metaplasia (IM) (Atrophy Club 2000) and finally gastrointestinal pathologists were able to obtain a higher level of interobserver consistency (8).

But the real keystone was the introduction of the OLGA system, born in Parma (7) when a restricted international group of experts in the gastroenterological field, pathologists and gastroenterologists of both sides of the ocean had a meeting to release a grading system that turn the simplicity, the reproducibility and, above all, the predictability of the lesions in its main strategies.

Currently, the degree of atrophy and metaplasia can be assessed according to the OLGA (the Operative Link for Gastritis Assessment) system that considers gastric atrophy as the lesion that indicates disease progression.

This system report gastritis in terms of stage organizing the histological phenotypes of gastritis along a scale of progressively increasing gastric cancer risk, from the lowest (OLGA stage 0) to the highest (OLGA stage IV). This staging framework is borrowed from the oncology vocabulary and it applies to gastritis a histology reporting format successfully adopted for chronic hepatitis too.

Gastritis is staged by combining the extent of atrophy (scored histologically) with its topographical location (resulting from the mapping protocol) (10).

As the Sydney System, OLGA system can be applied only when a full set of biopsy specimens is avail-

able. Recently the importance of this classification system has been strongly reiterated by the panel of experts gathered in Kyoto (8) with two important statements: statement 14A that establish that gastric cancer risk correlates with the severity and extent of atrophic gastritis with a strong grade of recommendation and high level of evidence (Consensus level: 94.7%) and statement 14B that claims that histological staging systems such as OLGA and OLGIM are useful for risk stratification, with a strong grade of recommendation but with low evidence level (Consensus level: 97.3%). The long course inflammation triggered by H.p. infection can exert a multistep pathway of precancerous lesions, in particular, atrophic gastritis, intestinal metaplasia and finally intraepithelial neoplasia. It is a common finding for an expert gastroenteropathologist, the association between presence of premalignant gastric lesions and presence of gastric cancer in a complete set of gastric biopsies and even more in surgical samples, showing that the risk to develop gastric cancer in a patient with premalignant lesions is nevertheless small, and that's why it is necessary the use of risk stratification methods. Gastric biopsy(ies) sampling can and must be used to provide the most important information for risk classification. Both OLGA staging system and its following modification OLGIM (Operative Link on Gastric Intestinal Metaplasia) staging system grades patients with gastritis into stages with a progressive risk of developing gastric cancer as the OLGA or OLGIM stage grows. The difference between the two systems is the evaluation of only intestinal metaplasia in the OLGIM system, improving in that way the interobserver reproducibility.

In the OLGA system the assessment of gastric atrophy is also extended to morphological findings that include every loss of appropriate glands with every following glandular substitution and, therefore, not only intestinal metaplasia, OLGA system result more adherent to real life, made of different facets of the pathology, even in the same patient. Long follow-up studies based had shown, with the proof of evidence, that OLGA systems showed a higher gastric cancer risk in patients in stage III or IV (10). As a logical effect, upper gastrointestinal endoscopic follow-up should be offered to patients that fall down in these subcategories.

Metaplasia

Metaplasia is the phenotypic replacement of one somatic, differentiated cell type with another differentiated somatic cell type in the tissue that is not normally present in that tissue, typically triggered by environmental stimuli which may act in concert with effects of H.p. infection and inflammation. A hallmark of metaplasia is a change in cellular identity and this process can be regulated by transcription factor that initiate and/or maintain cellular identity perhaps in concert with epigenetic reprogramming. Universally speaking, metaplasia is a precursor to low grade dysplasia which can culminate in high grade dysplasia and carcinoma. Improved clinical screening for and surveillance of metaplasia might lead to better prevention or early detection of dysplasia and cancer (8). High salt intake, low vegetables and fruit intake, low vitamin C intake, Helicobacter pylori infection, autoimmune gastritis can determine transition to columnar (gastric) cell towards intestinal cell type as transition in cell lineage. Intestinal metaplasia is a phenotypic change due to the replacement of gastric mucinous epithelial cells with goblet cells, enterocytes and colonocytes and it is easily detected in histopathologic findings, based on the markedly different cellular organization. It is a common feature in atrophic chronic H. pylori induced gastritis and increases in prevalence with disease duration. Intestinal metaplasia is considered to be an advanced stage of atrophy because the metaplastic glands replace the original glands and chronologically appear after the gastric glands are lost. This morphological aspect defines chronic atrophic gastritis as loss of appropriate glands. By adding the adjective appropriate (i.e. native to the specific area) to the original definition, metaplasia is incorporated in the definition of atrophy (9).

Different subtypes of intestinal metaplasia have been classified, on the basis of morphology and enzyme histochemistry into small intestinal and colonic types or complete and incomplete forms and using mucin histochemistry into three main types according to its morphology and glycoprotein content.

In type I which corresponds to complete, normal appearing small intestinal epithelium containing goblet cells producing sialomucins are interspersed among

absorptive enterocytes with eosinophilic cytoplasm (expressing the complete set of digestive enzymes such as sucrase and trehalase) and a 'brush border' given by large numbers of apical microvilli. Paneth cells may also been observed. The change does not appear to be abrupt but is progressive instead, as seen in the changing pattern of mucus secretion. The normal mucins of the stomach, MUC5AC at the surface and MUC6 in deeper glands, are pH neutral, and stained magenta with the periodic acid Schiff reagent. In intestinal metaplasia, acid mucins are observed with Alcian blue staining at pH 2.5, mostly sialic MUC2, and may be seen in the cytoplasm together with neutral mucins. Other metaplastic cells express only sialic acid mucins. (12). As the metaplastic changes advance and cover larger areas of the mucosa, new phenotypes are observed in some areas. In type II, a disorderly mixture of sialomucin-containing goblet cells are scattered among gastric-type cells containing either neutral mucin or sialomucins; type III, is characterized by tortuous and branched crypts lined by tall columnar cells containing abundant sulfomucins with smaller numbers of goblet cells containing either sialomucins or sulfomucins. (6). Both type II and type III are classified as incomplete or colonic type metaplasia because it resembles the large bowel phenotype in morphology and mucin expression, and also 'incomplete' because the set of digestive enzymes disappear partially or completely. Further, some patients may also re-express gastric (neutral) mucins. Incomplete metaplastic cells, like the normal colon epithelial cells, do not display a brush border and their mucin droplets are multiple and of variable size and shape. Gastric biopsy specimens with intestinal metaplasia frequently contain foci of both complete and incomplete metaplasia (mixed metaplasia). (12) Consistent data are available to demonstrate that the extent of gastric mucosa intestinalization parallels the histochemical demonstration of type II–III intestinal metaplasia (colonic-type metaplasia) (3) that have been shown to be associated with an increased risk of gastric cancer. However, from a practical point of view, the definition of the precise type of metaplasia in any single individual is limited by the fact that in extensive sampling are always present, though to differing degrees, both types of complete or incomplete metaplasia. The degree of incomplete intestinal metaplasia parallels the extent of intestinal metaplasia in general. Thus, there is a positive correlation between both the degree of incomplete intestinal metaplasia, and the degree of intestinal metaplasia in general, and the risk of progression to carcinoma. In addition to the type of metaplasia, the extension of atrophic/metaplastic changes is another determinant of gastric cancer risk. The presence and extent of intestinal metaplasia can also be easily evaluated with the use of specific mucin histochemical stains, such as Alcian blue/periodic acid–Schiff stain at pH 2.5. In routine histology, subtyping IM by applying specific histochemical stains is not recommended and have been largely replaced by immunohistochemical stains that identify proteins associated with particular mucin-encoding genes. Although more than 20 such mucin (MUC) genes have been identified, in practice, only a few (MUC1, MUC2, MUC5AC, and MUC6) are used routinely, and even those are used mainly in research settings. Because H. pylori does not normally adhere to intestinal-type epithelium, and because the organism usually disappears in mucosa with extensive intestinal metaplasia and atrophy, one theory is that intestinal metaplasia represents a host defense against H. pylori infection. Furthermore, changes in the composition of the gastric mucus in intestinalized epithelium may provide an additional source of defense against H. pylori, or alternatively, it may represent a type of physiologic adaptation to altered bacterial flora. The clonal nature of glands with intestinal metaplasia is debated. A recent study has suggested that gastric intestinal metaplasia is the result of a mutation and the metaplastic glands spread in the mucosa by crypt fission. In addition, there is also evidence in support of the clonal origin of gastric dysplasia from metaplasia. (12). Although intestinal metaplasia causes changes in stem and progenitor cells, it is not clear whether native gastric stem cells are the initial source of the changes and metaplasia results from their reprogramming into an intestinal type or if differentiated gastric cells first acquire intestinal properties and then stem cell properties. The stomach epithelium of mice converts readily into the intestinal type on transgenic expression of CDX2, a transcription factor that regulates intestinal development and differentiation. This observation indicates that intestinalization of gastric stem cells might be the initiating event in intestinal metaplasia (13).

Recently another type of metaplasia, the spasmolytic polypeptide-expressing metaplasia (SPEM) has been described. The gastric epithelium harbours chief cells at the base, underneath acid-producing parietal cells, progenitor cells (or stem cells) and then surface cells. H.p. infection can result in parietal cell loss. Moreover the inflammatory cells recruited by the presence of H.p. can produce cytokines stimulating INF-γ or TNF-α production that ultimately can produce, via TFF-2 (trefoil factor-2 or spasmolytic polypeptide), the appearing of SPEM. Alcian Blue staining is strongly positive in the abundant cytoplasmatic mucin of SPEM cell as well as MUC-6 immunostaining. However, more specific markers of SPEM are CD44 and Sox9. Histologically, SPEM of the Helicobacter infection models can be divided into two subtypes: mucous metaplasia and pseudopyloric metaplasia, morphologically distinct (14). SPEM has assumed a new role in the metaplasia- carcinoma sequence, since it might be a precursor to intestinal metaplasia, via foveolar hyperplasia and spasmolytic polypeptide-expressing metaplasia (SPEM) that, in turn it can give rise directly to gastric adenocarcinoma of intestinal type or indirectly, via a postulated trasformation in intestinal metaplasia. Both SPEM and IM are precursors to dysplasia and later adenocarcinoma.

Conclusion

For years, "gastritis" has been considered as a simple, though common and widespread inflammation of the stomach. The discovery of H.p. gave new stimulus to scientific research. In the attempt to find a shared common language that was understandable both for endoscopists, as well as for gastroenterologists and for pathologists too, but above all, useful for patients, the classification of Sidney and its subsequent revision took place over time. The main value of this classification was the production of a set of elementary lesions that combined with each other and based on the topographical distribution allowed the framing of gastritis in gradually increasing degrees of severity, which could be simply assessed using visual analogues. On the other hand, the main demerit was that not being perfectly reproducible and above all not allowing the stratification of the risk of gastric cancer development in the different patients, thus it didn't allowed a diversified and appropriate management to the "degree of illness".

The appearance of a classification system for gastritis, such as the OLGA staging system, immediately achieved this effect. Over time it has proved its validity also and especially when long follow-up periods have been considered. It is currently an accurate system for identifying a population with a greater risk of development of gastric carcinoma.

Recent data put gastric cancer among the top ten neoplasm and although the incidence of this type of cancer shows decreasing tendency, it is a frequent neoplasia, placed at sixth place, although with different frequencies in different geographical areas with a greater or lesser risk, and above all with an unfortunately, high incidence of mortality (source Globocan 2018).

Till from 1933, William Mayo stated that gastric cancer never arises in a healthy stomach (15) and now more than ever this affirmation become valid in the light of the results obtained with the application of a staging system for gastritis such as OLGA or OLGIM.

In fact, it must be noted that it is not so important the system used, OLGA rather than OLGIM or vice versa, but even better at least one of the two systems must be used and the pathologist must be confidant with the chosen system.

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