Y.-C. Zhang K. Kawai (Eds.)

Precancerous Conditions and Lesions of the Stomach

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Preface

The strategy adopted for the control of gastric cancer, involving both primary and secondary prevention, is very important. The development of epidemio-etiological studies and the adoption of many measures for reducing or blocking risk factors as well as increasing protective factors have reduced the incidence of gastric cancer in many countries. For example, in such countries as the USA and Finland, the incidence of gastric cancer has decreased strikingly during the last few decades. Even in Japan, whose people are among those at highest risk from this disease, the incidence of gastric cancer has decreased. In China, too (northeast China, a high risk area), the incidence of gastric cancer has tended to decrease in comparison with the situation that prevailed 15 years ago, according to recent reports.

Although the incidence of gastric cancer has decreased, or is decreasing, in many areas of the world, the background of the diseases to which gastric mucosa is subject, i.e., the different gastric diseases and precursors of gastric cancer, in inhabitants of the high risk areas in particular is not yet clearly known. Studies of precursors of gastric cancer are not merely of academic or theoretical importance, but are valuable in that they contribute to the development of primary prevention in practice.

In clinical practice, secondary prevention, i.e., early detection and early treatment, particulary the former, plays an important role at present. It is known, for example, that a 5-year survival rate after surgical treatment for early gastric cancer may be the result of early detection and early treatment made possible by advances in examination techniques. Studies on precursors of gastric cancer have also produced many useful contributions from pathologists and gastroenterologists. Many studies in this field have been published but the subject has not been fully clarified. I believe that the studies presented here may help in many ways to promote the early detection of gastric cancer.

In addition, conservative (including chemical) and surgical treatment for many precancerous conditions or precancerous lesions of the stomach are being carried out, and gratifying results have been achieved. In a sense, this has also played a primary prevention tole in gastric cancer. Follow-up studies of many precancerous lesions or gastric dysplasias have up to now been looked upon as important ways both of promoting early detection of

gastric cancer and clarifying the natural history of precancerous changes. In the author's experience, however, repeated endoscopic examinations and biopsies during follow-up for very small precancerous changes in the gastric mucosa have not been particularly successful as aids to the rediscovery and diagnosis of previously recognized lesions, except in the case of particular precancerous lesions, e.g., the protruding type or adenomatous type of gastric dysplasia. Therefore, it is necessary that more precise techniques or methods be developed for the study of these kinds of pathological changes of the gastric mucosa. It is expected that markers for detecting these pathological changes microscopically or even for endoscopic screening will be developed. More attention should be paid, too, to animal experiments involving the induction of precancerous changes in the stomach, as it has been reported by some authors that many previously unaccepted "causes" of precancerous change in the gastric mucosa are now accepted.

Another point which we believe to be significant is that different etiologic factors prevail in some of the different high risk areas of the world, while the mucosal changes, including the precancerous lesions and spectrum of gastric diseases of the inhabitants, probably differ also from area to area. Two high risk areas, Hokkaido in northern Japan and Liaodong Panisula in northeast China, serve as examples of this. A common findings in the gastric mucosae of the inhabitants of the former town is chronic gastritis with striking intestinal metaplasia, whereas in the latter town chronic gastritis with erosions and regenerations is prominent. This phenomenon affirms the need for geographic or epidemiologic pathological study of the precancerous changes of the stomach in order that the characteristics and natural history of these lesions of the stomach might be clarified.

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Addresses are given at the beginning of the respective contribution.

Contents

gastric polyp, Ménétrier's disease, gastric stump, etc., from which stomach cancers are likely to develop. The precancerous lesion, by contrast, is a pathological change, i.e., a change out of which stomach cancer may well develop. In other words, malignant transformation can occur in these lesions.

It is known that stomach cancer develops more frequently in precanceous conditions than in other gastric diseases because precancerous lesions usually exist with the former. Clinicians, therefore, regard the clinical assessment of the malignant potential of a precancerous condition in a patient as both desirable and practical. But one clinician's or pathologist's understanding of precancerous conditions and precancerous lesions sometimes differs from that of others. The precancerous condition, as a clinical concept, should be treated carefully as sometimes a precancerous lesion exists with in it. Chronic gastric ulcer was once looked upon as a common precancerous condition, whereas in recent years, controversy has surrounded its malignant potential; there are two very different views about whether or not, from this common condition, gastric cancer may develop. Chronic gastric ulcer was traditionally cited in many textbooks as being a precursor of gastric cancer. In recent years, however, many clinicians and pathologists have observed, on the basis of their own endoscopic and histopathological studies, that there is little or no inevitable relationship between chronic gastric ulcer and gastric cancer [16, 17, 19, 20]. It is necessary, therefore, to clarify this.

Most pathologists and clinicians know that chronic atrophic gastritis is one of the antecedants of gastric cancer [1, 16, 23]. Follow-up studies have revealed that in about 10% of patients suffering from chronic atrophic gastritis cancer has occurred during the following 10–20 years. What kind of histopathological changes, or, more concretely, what kind of epithelial changes, may lead to malignant transformation in chronic atrophic gastritis? From the pathologist's standpoint, detailed studies of this condition are his or her professional responsibility.

Intestinal metaplasia of gastric mucosa, usually accompanied by chronic atrophic gastritis, was traditionally looked upon as a precancerous lesion or precancerous condition [6, 25]. Since 1978, however, many types of intestinal metaplasia have been classified according to the characteristics of mucins secreted by the metaplastic epithelia; much enthusiasm was shown in this study field for a period of time. Now a majority of pathologists agree that the incomplete colonic type of intestinal metaplasia has a close relationship with gastric cancer, or they look upon it as a precancerous lesion [6, 22, 25]. Coincidentally, some types of intestinal metaplasia, e.g., type IIB of Jass (see Chap. 5, "Classification of IM"), usually showed frankly epithelial dysplasia and were classified as one type of gastric dysplasia.

Since the adenomatous and cryptal types of gastric dysplasia proposed by Zhang both consist of the intestinal type of epithelia, it is appropriate to correlate some types of intestinal metaplasia with gastric dysplasia.

As for the gastric polyp, its adenomatous type was reported by many authors to be subject to a greater degree of malignant change because of its lining of dysplastic epithelia, but recent reports have noted that malignant transformations were also found in hyperplastic polyps. It is not strange that dysplastic epithelia might exist in the latter [11, 12].

As explained in the literature, sumilarities between the adenomatous polyp (or adenoma) and the dysplasia of adenomatous type (or atypical epithelial lesion) sometimes confused readers because both of these pathologic conditions usually had protruded and well defined foci. Some of the latter, however, are in the form of flat elevated patches whereas the former are usually hemispherical and of a pedunculated polypoid shape macroscopically. While their naked shapes are somewhat different, their histopathologic attributes are alike. Adenomatous polyp and dysplasia of adenomatous type have similarities, then, but are not synonymous, e.g., some of the latter showed depressed shape macroscopically and microscopically.

Gastric dysplasia, or epithelial dysplasia of the stomach, is regarded as a precancerous lesion by most pathologists today. The pathologic changes associated with these dysplasias may be found in many conditions of the gastric mucosa and many types have been proposed [2, 5, 11, 13, 14, 16, 24, 31, 33].

Evaluation of the grade of atypism or the malignant potential of a dysplastic lesion is another problem for pathologists. Three grades have been used in practice: mild, moderate, and severe, or grades I, II, and III. In fact, these categories are somewhat artificial because a dysplastic change and its atypism are transitional. Therefore, grading for a given case of gastric dysplasia has usually varied from one pathologist to another and owed something to a particular pathologist's personal experience or understanding of these lesions, this despite the fact that many morphological descriptions for grading dysplastic changes have been cited in papers, booklets and textbooks. In a workshop on gastric dysplasia and related lesions held in San Miniato, Italy, by the International Study Group on Gastric Cancer (ISGGC) in 1982, many slides of gastric dysplasia contributed by participants were evaluated for grades of atypism by skilled pathologists in this study field [12]. Identical slides received different evaluations and gradings from different pathologists. In some cases one slide received separate evaluations ranging from nondysplasia, to severe dysplasia or even malignant lesion. This situation underlines the need for more objective criteria in the grading of gastric dysplasia.

In recent years, there have been two primary aspects in the search for objectivity in the grading of gastric dysplasias: (a) the attempt by many pathologists to find some markers specific to stomach cancer which will be useful for evaluating the atypism of gastric dysplasia, and (b) quantitative measurement of pathologic changes by morphometric techniques.

Immunohistochemical staining for some markers has been reported in evaluation of the atypism of gastric epithelia [3, 4, 28]. Some are such well

known antigens as carcino-embryonic antigens (CEA), ABH isoantigens, Lewis antigens, lectins, enzymes, and many laboratories' own antibodies (monoclonal or polyclonal) or biologic reagents. It was found, genereally, that the degree to which some of these markers expressed was consistent with the severity of atypism. Although the markers were not specific, in normal gastric epithelia they usually demonstrated polarity in the epithelial cells, while in malignant epithelia loss of polarity in the distribution of the markers was a common finding. Not all the markers reported were, however, sufficiently specific to be used as clinicopathological indexes for practically evaluating the grade of epithelial dysplasia.

With the advent of more advanced morphometric techniques, objective indexes for evaluating dysplastic grades have been proposed [27, 29, 30]. DNA content in normal epithelium, and cancer cell and its intermediate dysplastic epithelium, were measured by microspectrometry and flow cytometry. In the range of normal to dysplastic and malignant epithelia, except for the diploidy of normal epithelium, tetraploidy and aneuploidy are looked upon as signs of atypism or malignancy of the epitherlium, but there is usually overlapping of the various grades of dysplastic change, as is also the case with cancers. Some authors believe that if aneuploidy appears in a dysplastic lesion the malignant nature of the lesion is established.

Autoimage analysis systems have been used to evaluate grades of atypism of gastric dysplasia in recent years. Many quantitative measurement indexes for architectural and cellular atypism have been designed and are used in clinicopathological examination. These morphometric studies may at least help to standardize to a great extent, the objective criteria of gastric dysplasia.

Among the precursors of gastric cancer, environmental and host factors should be fully taken into account. Geographic/pathologic studies have revealed a relationship between some histopathologic types of stomach cancer and the patients' environments. For instance, more cases of intestinal-type stomach cancer have been occurring in high-risk areas despite its decrease at a faster rate than diffuse types of stomach cancer in other areas, due to improvements in variour environmental factors including diet. Since the diffuse types of stomach cancer have been maintaining their former incidence, the incidence of these cancers probably has little or nothing to do with environmental change [9, 15]. The author's recent comparative, etiologic and histopathologic studies of Chinese and Japanese people living in high risk areas of their respective countries [10, 32, 34], has revealed that one country's spectrum of gastric mucosal changes is different from the other's. Chronic gastritis with intestinal metaplasia was found more commonly in Japanese inhabitants, while in Chinese inhabitants active chronic gastritis accompanying epithelial degenerations and erosions was more striking. Gastric dysplasia of regenerative type was also striking in Chinese inhabitants. Therefore, I propose that in the study of the precursors of stomach cancer epidemiologic or geographic/pathologic factors should be considered fully.

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2 Precursors of Gastric Carcinoma*

P. Correa

Introduction

Two main histopathological types of gastric carcinoma have been identified, for which the names "intestinal" and "diffuse" have been coined [1]. The diffuse type is most frequently found in a mucosa which has a normal appearance outside the tumor. Although precancerous lesions have been described in some such cases, namely the "globoid dysplasia" [2] and the "nonmetaplastic dysplasia" [3], they are not found in most cases seen in general pathology practice.

Intestinal type tumors are surrounded by gastric mucosa showing chronic lesions which precede the carcinoma. These tumors are the subject of this chapter. Most intestinal type cancers make their appearance in a background of multifocal atrophic gastritis (MAG), whose sequelae include intestinal metaplasia and dysplasia [4]. MAG is the predominant type of chronic gastritis in countries whose inhabitants are at high risk from gastric cancer: Japan, China, Latin America, and Northern Europe. Another prominent form of atrophic gastritis, observed mostly in Scandinavian populations associated with the pernicious anemia syndrome, is diffuse corporal gastritis. Gastric cancer is also a late complication of gastrectomies, the so-called stump carcinoma. Very rare syndromes such as Ménétrier's gastritis, are occasionally seen as a background to gastric cancer. Gastric polyps may also give rise to carcinomas, especially the adenomatous polyps and less frequently the hyperplastic polyps.

Multifocal Chronic Atrophic Gastritis

It has been postulated that in the MAG syndrome a continuum of progressive changes precede clinical gastric carcinoma of the intestinal type. These changes are covered by the term "precursors" and fall into two basic

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categories: those with mature and those with immature cellular phenotype. Lesions with a mature cellular phenotype are probably remote from the cancer end point, are highly prevalent in populations at high risk, and probably do not deserve any special surveillance or intervention by clinicians because most will never reach the stage of clinical cancer. Cells in precursor lesions with immature phenotype may have reached the stage of irreversibility to normal phenotype, represent a greater threat to the patient, and deserve close clinical surveillance.

The MAG complex can be subdivided into several components which appear to occur sequentially in time and are briefly described and illustrated below. All components are accompanied by interstitial infiltration of chronic inflammatory cells, mostly lymphocytes and plasma cells which are abundant in younger patients but tend to become scarce with age and when the other components of the MAG complex become more advanced. Another common lesion observed in most stages of the MAG spectrum is hyperplasia of the glandular necks, which seems to wax and wane in response to recent epithelial cell injury.

Atrophy

Gland loss in MAG occurs as multiple foci, more common around the antrum–corpus junction and the lesser curvature. The loss of glands leaves wide areas of the mucosa occupied by the stromal elements of the organ (Fig. 1). The antral glands appear as multiple sections of a coil, at least four of which should be observed in a section which represents the full thickness of the mucosa. Mild degrees of atrophy are difficult to document and are based on a decrease in the number of gland loops. Such glands may disappear entirely from extensive areas when the atrophy is severe.

Intestinal Metaplasia

Gastric glands lost in the process of atrophic gastritis are frequently replaced by cells with intestinal phenotypes. Metaplastic glands replace the closely packed tubular glands of the corporal and antral mucosa by crypt-like structures lined by absorptive and goblet cells typical of the intestinal mucosa. Argentaffin and Paneth cells are also present in some intestinalized crypts. Metaplastic glands can also occupy the foveolar region and surface epithelium, especially when this region is thicker than normal, an apparent result of previous foveolar hyperplasia. Structures resembling both small and large intestinal mucosa have been identified in metaplastic lesions of the gastric mucosa (Figs. 2, 3). Some observations suggest that in the initial stages of metaplasia the small intestinal type predominates, whereas in advanced lesions colonic type crypts are more frequent [5–8]. The two

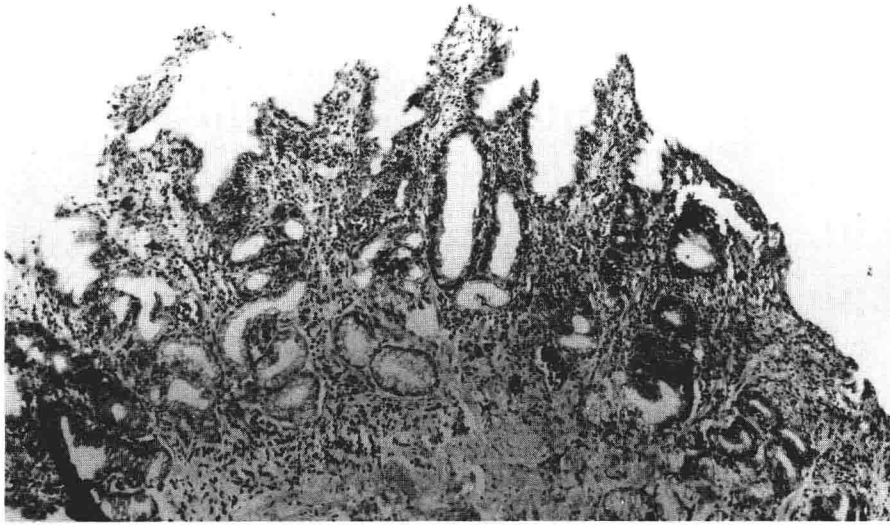

Fig. 1. Multifocal chronic atrophic gastritis (MAG). There is loss of antral glands, lymphocytic infiltrate, hyperplasia of gland necks, and depletion of mucin. Acute inflammation (activity) is superimposed on MAG

types often coexist, a situation that could be interpreted as a transition from small intestinal to colonic type. Cells of the small intestinal type of gastric metaplasia secrete the normal small intestinal sialomucin which stains with Alcian blue (pH 2.5) and does not take the high-iron diamine stain. The same cells usually secrete the complete set of intestinal enzymes: alkaline phosphatase, sucrase, leucine aminopeptidase, trehalase, succinic dehydrogenase, and diaphorase. For this reason, this type has been called "complete metaplasia" [9].

More advanced stages of the process often show the prominent colonic type of metaplasia, which has straight crypts lined by columnar cells with abundant cytoplasmic mucin, a brush border being absent (few microvilli). In this type of metaplastic mucosa, most small intestinal enzymes are absent, although sucrase and leucine aminopeptidase may persist in small amounts. For that reason, this metaplasia has been called "incomplete." The mucin secretion, a mixture of sialomucin and sulfated mucin, is typical of the large bowel; the latter stains positively with high-iron diamine. Several investigators, basing their reports on morphologic observations, have proposed that colonic metaplasia is more closely related to dysplasia and cancer than small intestinal metaplasia [5–8].

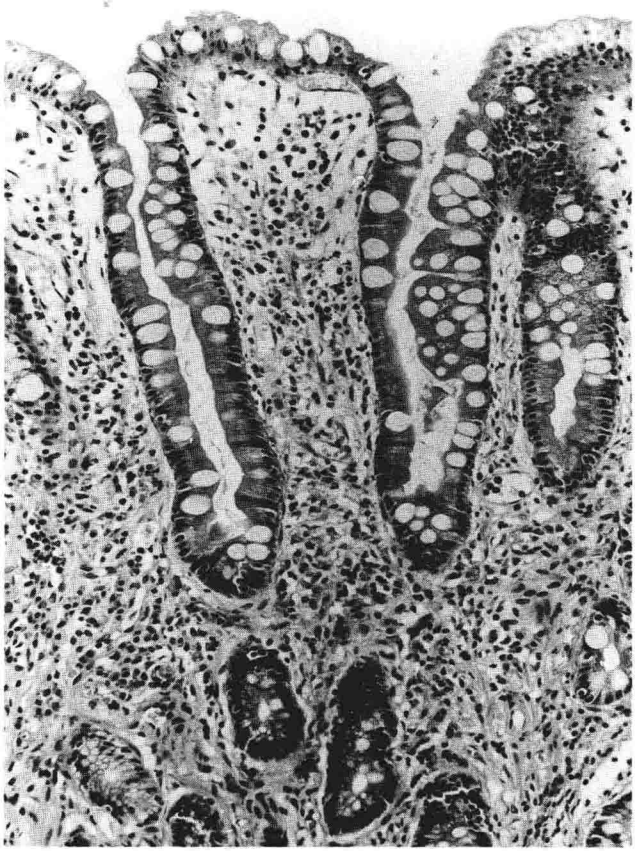

Fig. 2. Metaplasia of the small intestinal type. The surface is lined by absorptive cells with well formed brush border alternating with goblet cells

Dysplasia

The most frequent form of dysplasia in patients with MAG consists of proliferation of closely packed tubular glands which do not produce a gross elevation of the mucosa. This lesion has received the names "atypical epithelium" [10], "adenomatous dysplasia" [11] and "type I dysplasia" [12] (Fig. 4). The glands contain large, elongated, hyperchromatic nuclei which overlap one another in sections stained with hematoxylin and eosin. In mild dysplasias, the nuclei are mostly basal and elongated in shape. In moderate forms of dysplasia, the nuclei are closely packed, elongated, and pseudostratified, but retain some degree of polarity. In severe dysplasia, polarity is partially or totally lost, and the nuclei are oval or irregularly