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P53 and PCNA expression in glandular dilatation of gastric mucosa

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Abstract

AIM: To study the expression of p53 and PCNA in relation to gastric mucosa lesions.

METHODS: The S-P immunohistochemical method was used to observe 92 samples of glandular dilatation of gastric mucosa and 30 cases of adenocarcinoma of the stomach.

RESULTS: P53 showed no expression in simple glandular dilatation, but positive expression in a small number of cells in atypical glandular dilatation (< 8.6%, 5/58) as well as strong expression in gastric glandular cancer (< 46.7%, 14/30). There were a small number of PCNA positive cells in simple glandular dilatation, and a significant increase of positive cells in atypical glandular dilatation ($P < 0.01$); the positive cells were widely distributed and deeply stained in the cases of gastric cancer.

CONCLUSION: P53 and PCNA may be jointly used as an important criterion for diagnosing, classifying and treating the precancerous lesions of gastric mucosa.

Key words: Gastric mucosa; Precancerous conditions; Stomach neoplasms; Adenocarcinoma; Genes, P53

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INTRODUCTION

In recent years, there has been much research attention paid to the glandular dilatation of gastric mucosa. It was proposed that some morphological forms of gastric glandular dilatation are related to gastric cancer, but other authors suggested that the cystic dilatation of various degrees in gastric and pyloric glands is only a kind of alteration that occurs in the late stage of atrophic gastritis[1-7]. The glandular dilatation of gastric mucosa is commonly seen in clinical pathology, so it is necessary to distinguish the types of glandular dilatation and determine the pathologic forms that are involved in the cancerous lesions. In this study, the S-P immunohistochemical method was used to perform a comparison between 92 samples of different histologic types of glandular dilatation and 30 cases of adenocarcinoma of the stomach. The results from assessment of p53 and PCNA expression will contribute to the clinical treatment and research of precancerous lesions.

MATERIALS AND METHODS

In total, 122 samples of gastric mucosa biopsy were observed. Among them, 92 were gastric mucosa glandular dilatation and 30 were adenocarcinoma of the stomach. The patients ranged in age from 25 to 74 years old, with an average age of 49.3 years. There were 72 males and 50 females. The samples were fixed in 10% formalin, embedded in paraffin, and sectioned to 5 μm in thickness. After standard hematoxylin-eosin (HE) staining, cell morphology and tissue structure were observed. Immunohistochemical staining was carried out by linking the streptomyces avidin and peroxidase agents. Anti-p53 monoclonal-antibodies (DO-7, reactive with both wild type and mutant proteins), anti-PCNA and instant-type reagent boxes were all the products of the Maixi Biochemical Technology Company. DAB coloration and hematoxylin staining were used, with PBS serving as the first antibody to make negative comparison. The positive reactions were graded according to the number of brown particles appearing in the cell nucleus: Ⅰ, 0%-25%; Ⅱ, 26%-50%; Ⅲ, 51%-75%; Ⅳ, 76%-100%.

The simple and heterotype dilatations were distinguishable; the latter included the cystadenomatoid and adenomatoid atypical hyperplasia, in accordance with the degree, form and number of the glandular dilatation, and the amount of mucus in the lumen of gland, the presence of atypical epithelioglandular cells, as well as the accompanying glandular atrophy and/or intestinal metaplasia, *etc*.

RESULTS

Histopathology

Simple glandular dilatation was found in a small number of cases with mild degree of focal or isolated glandular dilatation, showing an increased amount of mucus in the lumen of the gland. The epithelioglandular cells appeared as monolayer pavement or columnar in shape; there were no atypical alterations of the

Table 1 P53 and PCNA expression in 122 cases of gastric mucosa biopsy

Type	Number of cases	P53 expression					PCNA expression				
		-	Ⅰ	Ⅱ	Ⅲ	Ⅳ	Positive cases	Ⅳ	Ⅰ	Ⅱ	Ⅲ
Simple dilatation	34	0	0	0	0	0	31 (91.2)	3 (8.8)	0	0	
Heterotype dilatation	27	25	2	0	0	0	2 (7.4)	4 (14.8)	14 (51.9)	9 (333)	0
Cystadenomatoid Adenomatoid	31	28	3	0	0	0	3 (9.7)	1 (3.2)	13 (41.9)	15 (48.4)	2 (6.5)
Glandular cancer	30	16	1	3	5	7	14 (46.7)	9	2 (6.7)	4 (13.3)	21 (70.0)

epithelium and no accompanying glandular atrophy or intestinal metaplasia. Atypical glandular dilatation showed cystadeno- and adenomatoid atypical hyperplasia.

The cystadeno-atypical proliferation showed extensive glandular hyperplasia in cystic dilatation, of various degrees and forms, with possibly papilla-like or branch-like structures, irregularly dilated glands, and large diameters of several- or dozens-times that of the ones with smaller diameters. Epithelial cells showed a monolayer or multilayer arrangement. Most atypical hyperplasia showed a decrease in amount of mucus in the lumen of the gland, accompanied by some degree of glandular atrophy in most cases and/or with intestinal metaplasia.

The adenomatoid atypical hyperplasia showed glands that were dilated to a moderate degree, 4- to 6-times that of the normal size, clustered in groups, and distributed in a back-to-back or conjugated pattern. There was a possible presence of intraglandular cannula[7]. Decreased interstitial and epithelioglandular cells in monolayer or stratified arrangement were noted, as was decreased lumen of the gland; there was also possibly accompanying glandular atrophy to various degrees, with or without intestinal metaplasia.

Immunohistochemical staining showed no p53 expression in simple glandular dilatation but positive expression (8.6%, 5/58) in heterotypical glandular dilatation. The pattern of positive expression demonstrated a focal expression or expression in some cells of some dilated glandular ducts, but no positive expression in many glandular ducts located in the same area; the staining density was weak grade Ⅰ positive expression. For the detected expression in adenocarcinoma, the positive expression was strong, widely distributed and with deep staining, pertaining to grade Ⅲ or grade Ⅳ. The PCNA positive expression in simple glandular dilatation was less extensive, mostly corresponding to grade Ⅰ, while that in heterotype dilatation involved obviously more cells, mostly corresponding to grade Ⅱ or grade Ⅲ, presenting a positive expression of many glandular ducts in one area. The positive expression of PCNA in adenocarcinoma was widely distributed, with rather deep staining, mostly corresponding to an expression of grade Ⅲ and grade Ⅳ (Table 1).

DISCUSSION

Glandular dilatation of gastric mucosa may be due to many diseases, such as chronic atrophic gastritis[8], gastric polyp[3], chronic ulcer[9], chronic superficial gastritis and the presence of cancerous gland[10], all of which may be observed characteristically in gastric mucosa biopsy. While it is not a primary disease itself, it presents with different degrees, forms and numbers. Hence, it has been suggested that the cystic dilatation of the gastric gland and pyloric gland in deep mucosa covered by the pavement of epithelial cells should be a sign of alteration of a denatured or atrophic gastritis in the advanced stage, and also that the cystic dilatations occurring in 95% of the early stage gastric cancers could be closely associated with the cancerous formation. Some reports have dealt with the naming of terms, such as cystadeno dilatation and gastric adenocyst[4,11]. We believe that in a case simply involving the cystic dilatation of glands and inflammatory infiltration, the dilated glands are small in number and mild in degree, the possible definition may be simple glandular dilatation caused by an inflammation or a compression in the ducts, not belonging to a precancerous lesion. However, in a case of cystic dilatation, inflammatory infiltration, and dilated glands with great numbers and severe degrees of various forms, with epithelioglandular cells in monolayer or stratified arrangement, and nuclei of various sizes, this kind of dilatation would be called the cystadeno-atypical hyperplasia because of its cystadeno-structure and atypical epithelium; this form is recognized as an important precancerous lesion. As for adenomatoid atypical hyperplasia, on which there had been few reports, the dilated glands are 4- to 6-times that of normal glands in number, cluster in groups, and show interstitial decrease, back-to-back or conjugation position, and epithelioglandular cells displaying atypical hyperplasia accompanied by glandular atrophy or intestinal metaplasia to various degrees. Because of its adenomatoid structure and epithelium atypical hyperplasia, this form is called adenomatoid atypical hyperplasia, another important feature of the precancerous lesion.

The wild type *p53* gene encodes a tumor suppressor and plays a role in control of cell differentiation and prevention of abnormal growth of cells. Because of its short and unstable half-life, and its low concentration in cells, it can not be detected by immunohistochemical examinations. The product of the mutant *p53* gene, however, is a more stable protein that accumulates in cells; its loss of normal function includes extension of its half-life, which may inactivate the wild type p53. The immunohistochemical assessment of mutant p53 has thus become a standard tool to research genetic alteration of a tumor. People who present with excessive p53 protein expression in benign lesions accompanied by severe degree, non-typical epithelium hyperplasia, have been subsequently proven to have a cancerous lesion, suggesting that there should be alteration of cells in some precancerous lesions, which can be expressed (and detectable) at the protein level[12]. The expression detected in samples of gastric mucosa biopsy of our study is consistent with that in previous reports. Five cases of atypical glandular dilatation of gastric mucosa showed positive expression, but the positive cells were focal in distribution; the simple dilatation displayed no expression. The comparison between atypical glandular dilatation and adenocarcinoma of stomach shows a significant difference ($P < 0.01$), indicating that p53 occurs in a great number of cells only after occurrence of malignant alteration of the cells and a transformation from gastric mucosa to cancer. Thus, this event plays a role of great significance in formation of early cancer.

PCNA is a kind of 36 Mr nucleoprotein, related to the synthesis of DNA in the cell cycle. It seems that cells can remain in an active proliferation state, which at present has been used as a criterion for assessment of malignant potential of a tumor in the precancerous stage and of the dynamics of tumor cells. In this series of 92 samples of biopsy, the expression in glandular dilatation of gastric mucosa was found to be increased along with the rise in the active level of cell proliferation. The comparison between the simple glandular dilatation and the atypical one showed significant difference ($P < 0.01$). In gastric cancer, the positive expression is widely distributed and deep in tinction. PCNA is an important criterion for the diagnosis, classification and treatment of precancerous lesion.

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