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미만형 위암의 전암성 병변으로서의 비화생이형성

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Non-Metaplastic Dysplasia as precursor lesion of Diffuse type stomach carcinoma

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Abstract

Background : This study was performed to investigate the relationship of types of dysplasia and histologic types in 141 cases of surgical specimens of early gastric cancer. **Material and methods** : Fromalin-fixed and paraffin-embedded gastric mucosa and cancer tissue from 141 patients with gastric cancer *underwent gastrectomy were studided* with classification of gasric cancer by Lauren and dysplasia. **Results** : The histologic types by Lauren1) were: diffuse type 59 cases (41.84%); intermediate type 41 cases (29.08%); and intestinal type 41 cases (29.08%). The types of gastric dysplasia in gastric mucosa adjacent to the tumor were classified *into nonmetaplastic dysplasia* 98 *cases* (69.50%) and metaplastic dysplasia 97 cases (68.8%). Simultaneous presentation of both dysplasias was 55 cases (39.00%). The frequency of nonmetaplastic dysplasia in diffuse and intermediate type carcinoma was significantly higher than in intestinal type carcinoma ($p<0.05$), and the frequency of *metaplastic dysplasia in intestinal type carcinoma* was significantly higher than that of diffuse and intermediate carcinoma ($p<0.05$). In cases of metaplastic dysplasia, age and frequency and severity showed positive correlation ($p<0.05$). **Conclusions** : These results suggest that types of dysplasias may be related to two different pathways *in human stomach carcinogenesis. And we propose a hypothesis* that nonmetaplastic dysplasia and diffuse type adenocarcinoma sequence may be possible in the development of diffuse type of stomach cancer.

Key words : Sastric Cancer, Dysplasia, Non-metaplastic, Lauren classification

INTRODUCTION

Gastric epithelial dysplasia (GED) has been reconized as the main precancerous lesion. [2-6] But the concept and the scope of GED has involved some questions and problems7), such as the natural evolution in a biologic sense and clinical management of patients with these histologic changes. Jass8) has speculated about the possible heterogeneity of GED. Ming[9]also recognized two types of dysplasia; one as dysplasia of metaplastic epithelium and the other as dysplasia of nonmetaplastic epithelium. A large body of literature is available on the dysplasia of intestinal type carcinoma.[2-6,9,11] However, neither the cell of origin nor the precursor stages of diffuse carcinoma have not yet been documented. Ghandur-Mnaymneh[10] defined nonmetaplastic dysplasia as replacement of the differentiated cell lining the glands by undifferentiated cells with varying degrees of cytologic abnormalities and

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cellular pleomorphism, but with absence of architectural glandular derangements. And the severity of the changes was graded by the extent of involvement of gland (crypt) as measured from proliferative zone and the degree of cytological abnormalities. He tried to correlate this type of dysplasia to gastric cancer. Contary to American or European populations, gastric cancer is the most common neoplasm in Korea. And once precancerous changes are identified, their elimination may serve to prevent the occurrence of possible gastric cancer, in addition to extending our knowledge of different pathways of gastric carcinogenesis. With these basis, we attempted to evaluate classification and prevalence of types of GED to elucidate the relationship between dysplasia and types of gastric carcinomas in Korean.

MATERIALS AND METHODS

The materials were141 cases of surgical specimens of early gastric cancer submitted to Department of Pathology following gastrectomy. The histologic types of the tumor were classified into diffuse, intermediate, and intestinal type, according to Lauren's criteria, consulting with Guidlines for Pathologic Study of Gastric Cancer proposed by the Study Group for Gastrointestinal Pathology, Korean Society for Pathologists. The types of gastric dysplasia in gastric mucosa adjacent to EGC lesions were classified by the proposed standard of Ghandur-Mnaymneh into metaplastic and nonmetaplastic dysplasia. The severity of the changes was graded by the criteria of Ghandur-Mnaymneh in nonmetaplastic dysplasia and the proposal of WHO expert committee in metaplastic dysplasia.

RESULTS

1. The histologic types and incidence of 141 cases of early gastric cancer (EGC) by Lauren were: diffuse type 59 cases (41.84%); intermediate type 41 cases (29.08%); and intestinal type 41 cases (29.08%). The mean age for the histologic types was 49 years in diffuse type, 51 years in intermediate type, and 54 years in intestinal type. Mean age of EGC overall was 51 years.

2. The types of gastric dysplasia in gastric mucosa adjacent to EGC lesions were classified as nonmetaplastic dysplasia (98 cases:69.50%) and metaplastic dysplasia (97 cases: 68.8%). Among these, the cases of simultaneous presentation of both dysplasias were 55 cases (39.00%) (Table 1.).

Table 1. Frequency of types of gastric dysplasia in 141 cases of EGC

	types of dysplasia			
frequency	metaplastic(%)	nonmetaplastic(%)	both(%)	total
positive	42(29.79)	43(30.50%)	55(39.00)	141(100%)

The cases showing severity of more than moderate degree were 82 cases (58.20%) in metaplastic dysplasia and 86 cases (60.99%) in nonmetaplastic dysplasia (Table 2.).

Table 2. Association of histologic types of EGC with two types of dysplasia

Histologic types of EGC	Total number	Types of Dysplasia	Prevalence of dysplasia 0	1	2	3
Diffuse	59	M	26(44.1)	12(20.3)	12(20.3)	9 (15.3)
		N*	8(13.6)	4(6.8)	24(40.7)	23(40.0)
Intermediate	41	M	16(39.0)	2(4.9)	13(31.7)	10(24.4)
		N*	2(4.9)	7(17.1)	13(31.7)	19(46.3)
Intestinal	41	M*	2(4.9)	1(2.4)	5(12.2)	33(80.3)
		N	33(80.5)	1(2.4)	4(9.8)	3(7.3)

M: metaplastic dysplasia, N: non-metaplastic dysplasia, 0;absence of dysplasia,
1: mild, 2: moderate, 3: severe degree of dysplasia
(*: $p < 0.0001$)

3. In cases of metaplastic dysplasia, age and frequency and

severity showed positive correlation (Table 3.).

Table 3. Prevalence of EGC and dysplasias by sex and age group

Sex/ Age	Total No.	types of tumor D	Inter	Intest	meta. dysplasia I	2	3	nonmeta. dysplasia 1	2	3
Males										
<=35	12	6	4	2	3	5	2	1	0	7
36-50	34	13	14	7	4	10	11	4	12	11
>50	50	17	16	17	2	7	22	5	14	12
Females										
<=35	4	4	0	0	2	0	1	1	1	1
36-50	14	5	2	7	1	0	7	1	1	1
>50	27	5	8	3	3	6	9	0	11	10

No.: numbers, D; diffuse, Inter; intermediate, Intest; intestinal,
meta; metaplastic, nonmeta; nonmetaplastic,
1: mild, 2: moderate, 3: severe degree of dysplasia

4. In relationship of histologic types of EGC and types of gastric dysplasia, the frequency of nonmetaplastic dysplasia in diffuse and intermediate type carcinoma was significantly higher than the corresponding frequency in intestinal type carcinoma, and the frequency of metaplastic dysplasia in intestinal type carcinoma was significantly higher than corresponding frequency of diffuse and intermediate carcinoma.

5. The frequency and severity of metaplastic dysplasia of intermediate type carcinoma was between diffuse type and intestinal type carcinoma, but in frequency and severity, no significant difference in nonmetaplastic dysplasia from diffuse type carcinoma was seen.

Discussion

Gastric carcinogenesis is a multistep phenomenon, beginning with precancerous conditions. Among these, adenoma is a direct precursor, because of dysplastic nature of its cells. Hence , dysplasia has shared the meaning of adenoma. In this study, dysplasia implicate adenoma. Ming mentioned dysplasia involving metaplastic and non-metaplastic glands of stomach.[9] The intestinal type stomach cancer is known as developed from intestinal type dysplasia, however, the diffuse type is known as 'de novo' cancer without precuror lesion. Ghandur-Mnaymneh *(GM)*[10] *proposed " non-metaplastic dysplasia of gastric carcinoma".* The main feature of the dysplasia by GM[10] is replacement of the differentiated cells lining the glands by undifferentiated cells with varying degrees of cytologic abnormalitites and cellular pleomorphism, but with absence of architectural glandular derangement. This definition is justified by cytokinetics and histologic observations in experimental gastric carcinogenesis and early human gastric carcinoma. In this study the grading of severity in dysplasia was done by GM's.[10] Mucosa exhibiting unequivocal cytologic features ofglands with cellular and nuclear pleomorphism was classified as positive for dysplasia. This was classified with mild, moderate, severe dysplasia utilizing the modification of Jass's. [8] The severity was graded by the extent of involvement of the *crypt and glands as measured from the proliferating* zone(PZ) and cytologic abnormalities. In this study, the types of gastric dysplasia in gastric mucosa adjacent to the *tumor were classified into nonmetaplastic dysplasia* 98 cases (69.50%) and metaplastic dysplasia 97 cases (68.8%). Simultaneous presentation of both dysplasias was 55 cases *(39.00%). This data is similar to the GM's.*[10] In GM' study, the severity of dysplasia was graded by low and high-grades.[10] The curretnt study showed that the frequency of nonmetaplastic dysplasia in diffuse and intermediate type carcinoma was significantly higher than in intestinal type carcinoma($p<0.05$), and the frequency of metaplastic dysplasia in intestinal type carcinoma was significantly higher than that of diffuse and intermediate carcinoma ($p<0.05$). In cases of metaplastic dysplasia, age and frequency and severity showed positive correlation ($p<0.05$). These results are also accordant with the GM's. Interestingly, this data can explain the coexistance of diffuse and intestinal tyes in one tumor of same patient. According to our results, types of dysplasias are related to the two different pathways in human stomach

carcinogenesis. And we propose a hypothesis that nonmetaplastic dysplasia and diffuse type adenocarcinoma sequence may be possible in the development of diffuse type of stomach cancer. If we accept the nonmetaplastic dysplasia-diffuse type carcinoma sequence, we can manage the diffuse type stomach cancer blocking the step from dysplasia to carcinoma of diffuse type. Our results showed the mean age of nonmetaplastic dysplasia was younger than that of intestinal types. Although the most important etiologic factor associated with intestinal type dysplasia is well known as H.pylori, there is a report that diffuse type carcinoma is also associated with H.pylori by directly promoting diffuse type cancer or inducing the cascade of molecular events.[12] But the Nardone's proposal [12] needs verification through further studies.

The diffuse type carcinoma has been known as its development in younger than intestinal type. Our results can support this. Since there are few report about nonmetaplastic dysplasia-diffuse type carcinoma except for GM's, the further studiesincluding genetic and molecular studies will be needed to verify our hypothesis. In addition, the efforts to find the environment for developing or triggering nonmetaplastic dysplasia will be very useful to elucidate the nature of diffuse type.

Conclusion

These results suggest that types of dysplasias are related to the two different pathways in human stomach carcinogenesis. And we propose a hypothesis that nonmetaplastic dysplasia and diffuse type adenocarcinoma sequence may be possible in the development of diffuse type of stomach cancer. This proposal should be verified in further studies with on a larger series of cases, including investigations of molecular level.

REFERENCES

1. Lauren P, The two histological main types of gastric carcinoma. Diffuse and so-called intestinal type carcinoma. Acta.Path. et Microbiol.Scandinav. 64: 31-49, 1965
2. Nagayo T, Histological diagnosis of biopsied gastric mucosa with special reference to that of borderline lesions. Gann Monogr Cancer Res 11: 245-256, 1971
3. Cuello C, Correa P, Zarama G, Lopez J, Murray J, Cordillo G, Histopathology of gastric dysplasia, correlation with gastric juice chemistry. Am J Surg Pathol 3: 491-500, 1979
4. Kunze E, Schauer A, Eder M, Seefeldt C, Early sequential lesions during development of gastric cancer with special reference to dysplasia. J Cancer Res Clin Oncol 95: 247-264, 1979
5. Morson BC, Sobin LH, Grudmann E, Johansen A, Nagayo T, and Serck-Hanssen A. Precancerous conditions and epithelial dysplasia in the stomach. J Clin Pathol 33: 711-721, 1980
6. Antonioli D, Goldman H, Appelman H, Kaufman N. Gastric carcinoma and its precursors. Gastrointestinal Pathology, Baltimore, Williams & Wilkins, 1990
7. Saraga EP, Gardiol D, Costa J. Gastric dysplasia. A histological follow-up study. Am J Surg Pathol 11: 788-796, 1987
8. Jass JR, A classification of gastric dysplasia. Histopathology 7: 181-193,1983
9. Ming SC, Bajtal A, Corren P, Munoz, Nagayo T and Stemmerman GN, Gastric dysplasia. Significance and pathologic criteria. Cancer 54: 1794-1801, 1984
10. Ghandur-Mnaymneh, Jose P, Roldan E, and Cassdy J, Dysplasia of nonmetaplastic gastric mucosa. Am J Surg Pathol 12(2):96-114, 1988
11. Hattori T, Development of adenocarcinomas in stomach cancer. Cancer 57 1528-1534, 1986
12. Nardone G, Rocco A. Malfertheiner P. Helicobacter pylori and molecular events in precancerous gastric lesions. Aliment Pharmacol Ther1:261-70, 2004

국문요약

배경및 목적 : 장형 위암의 전암성 병변으로는 화생이형성이 잘 알려져 있고, H.pylori와의 연관성도 설명되고 있으나, 미만형 위암은 전암성 병변이 없는 것으로 알려져 왔다. 본연구는 위암의 전암성 병변으로서 병리학적으로 화생이형성과 비화생이형성을 정의하고 임상적으로 위암의 조직학적 유형과의 관련성을 규명하는 데 있다. **재료 및 방법 :** 141예의 포르말린에 고정되고, 파라핀에 포매된 조기위암으로 진단된 환지의 암조직과 인접한 비종양성 위점막 조직을 현미경으로 재 검색하여, 암은 Lauren 분류를 이용하여 분류하였고, 인접 비종양 점막은 화생과 비화생이형성으로 분류하고, 3등급으로 심한 정도를 분류하였다. **결과 :** 미만형이 59예(41.84%), 중간형이 41예(29.08%), 장형이 41예(29.08%) 였다. 비

화생이형성이 98예(69.50%)이고, 화생이형성이 97(68.8%)였다. 두이형성이 공존하는 예는 55예(39%)였다. 미만형과 중간형에서 비화생이형성의 빈도는 장형보다 높았으며, 장형암에서 장형이형성의 빈도는 다른 두형에서보다 높았다. 장형이형성의 경우 나이와 발현 빈도와 심한 정도는 비례관계를 나타내었다. 결론 : 위암의 발생과정에는 두가지 이형성이 존재하며 비화생이형성은 미만형 위암의 발달에서 전암성 단계의 병변으로 인정된다.