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Atypical glands in gastric adenoma

Three-dimensional architecture compared with carcinomatous and metaplastic glands*

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Summary. The pathogenetic relationship of gastric adenoma to carcinoma remains unsettled, partly due to the difficulty in discriminating between the atypical tubules of adenoma and those of adenocarcinoma. Although it has been said that this discrimination should depend not only on cellular changes but also on disorganization of glands, the latter has not been described in accurate morphological terms. In view of this, gastrectomy specimens from three patients with tubular adenoma were submitted to graphic reconstruction of atypical glands from serial sections, and were compared with well differentiated adenocarcinoma and metaplastic mucosa. Reconstruction disclosed that in adenoma, unlike in metaplastic mucosa, atypical tubules had multiple connections with adjacent ones, forming a network. At some sites of anastomosis the lumen was also connected. Though this pattern was similar to that of well differentiated adenocarcinoma, the meshes of the network were much more coarse than in the latter, showing that adenoma was a mere miniature of adenocarcinoma. The porous structure, the commonest architecture of adenocarcinoma, was never found in adenoma. There were in addition giant glands with complicated branching which, together with microcysts forming at mucosal bottom, caused convolution and twisting of tubules, producing those abnormal patterns in section on which too much stress is placed.

Key words: Gastric adenoma – Gastric carcinoma – 3-D structure – Dysplasia

Although gastric adenoma is today a definite pathological entity, its malignant potential still remains unsettled. In Japan, most adenomas detected

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in group examination are of the type classified as flat (Ming 1977) or tubular adenoma (Ohta and Sobin 1977; Morson and Dawson 1979), which in this country has been called an atypical epithelial lesion on account of more or less dysplastic change in tubular epithelium (Sugano et al. 1971). Nagayo (1966 and 1971) suggested its borderline malignant character when he separated it from protruding or elevated types of early gastric carcinoma. Long-term follow-up studies, however, have increasingly convinced most Japanese gastroenterologists that tubular adenoma either remains dormant or evolves very slowly, and the development of cancer from it, even if present, may be exceptional (Fukuchi and Mochizuki 1982). These findings are not consistent with the investigation of Ming (1965) who estimated the incidence of malignant change of adenoma at the incomparably higher percentage of 40%.

Such a discrepancy may be ascribed to different types of lesions studied, but also implies that the differentiation of this tumor from adenocarcinoma is not fully understood. Thus it sometimes occurs in Japan that a case, once reported as showing malignant change in a previously benign adenoma, is subsequently considered to have been an early gastric carcinoma already at the time of the first biopsy. In fact, some adenomas closely simulate early, well differentiated adenocarcinoma, both macroscopically and microscopically. Diagnosis and treatment of gastric adenoma will be associated with this sort of difficulty and remain ambiguous unless reliable morphologic criteria are established.

Obviously, it is not only on cytological basis that gastric adenocarcinomas are discriminated from precancerous lesions; the structural disorganization of glands also serves as another important key to differentiation. In fact, the diagnostic value of the latter feature has been pointed out and emphasized several times (Schwalbe 1911; Böhmig 1935 and 1937; Monaco et al. 1962; Ohta 1964; Nagayo 1966; Jap. Res. Soc. Gastric Cancer 1974; Grundmann 1975; Morson et al. 1980; Grundmann and Schlake 1982). Even so, the pattern of "carcinomatous glands" (Hendrickson and Kempson 1980) had not been defined in strict 3-D morphological terms until, in a recent reconstruction study, the present authors managed to establish the basic skeleton of gastric adenocarcinomas (Takahashi and Iwama: Three-dimensional morphology of gastric adenocarcinoma. Atypical glands as a basis for histopathologic diagnosis, submitted to Virchows Arch [Pathol Anat]). The present article outlines our study in which 3-D structural analyses are extended into gastric adenomas in comparison with adenocarcinoma. This will illuminate how and in what aspect the architecture of adenoma is different from that of overtly carcinomatous glands.

Material and methods

Gastrectomy specimens from three patients with tubular adenoma were selected from the surgical material of the Department of Pathology, Tohoku University Hospital (Table 1). All the tumors were found in antrum and presented as a flat mucosal elevation which harbored more or less atypical tubules growing in the superficial zone (Fig. 1A). In Cases 1 and 2 of the series the lesion was interpreted as being less advanced than in Case 3 in which, unlike the others, the tumor exceeded 2 cm in diameter with more pronounced epithelial dysplasia. The estimation of stromal volume density (V_{vs}) by microscopic point counting produced a

Table 1

	Age, sex	Site	Largest diameter	Volume density of Stroma (V_{vs})	Coexistent carcinoma
Case 1	62, m	Antrum Lesser curve	1.6 cm	0.358	yes
Case 2	66, m	Antrum Lesser curve	2.0 cm	0.371	no
Case 3	61, m	Antrum Anterior wall	2.8 cm	0.233	no

much lower value for Case 3, indicating a state of close packing of tubules growing actively in lamina propria (Table 1). This tumor, however, was still sufficiently distinguishable from adenocarcinoma on histological basis.

The architecture of adenoma was compared with that of well differentiated adenocarcinoma. The latter had been established in our foregoing reconstruction, and the results in that study were used for this comparison. The wording of well differentiated adenocarcinoma was used to conform to the Japanese classification of gastric cancer (Jpn Res. Soc. Gastric Cancer), and this roughly corresponded to the intestinal (Lauren 1965) or tubular (Grundmann and Schlake) type. In addition, gastric mucosa with advanced metaplastic gastritis was used to examine a condition predisposing to development of adenoma; a stomach removed for chronic ulcer was selected for analysis, with antral mucosa showing almost complete replacement of glands by intestinal epithelia.

After fixation by formalin, the portion of the gastric wall containing an adenoma was cut in the ordinary way into parallel slices, and these were processed to paraffin embedding. On HE-stained sections of these, the area that appeared most appropriate for reconstruction was determined, and the tissue block including this area was re-embedded in celloidin-paraffin for serial sectioning. Two hundred serial sections were made from each tumor at 3.5 μ in thickness of a single section, and were stained with Azan-Mallory method.

Reconstruction was performed by a graphic method as follows. An area selected for reconstruction in one of a set of serial sections was magnified and projected onto a sheet of tracing paper by use of a profile projector (Nikon, model V-16C). We made it a rule to reproduce an area of mucosa not smaller than 4 mm in breadth, covering the total depth of mucosal layer. On the tracing paper, the linear boundaries of all tubular structures in the area were faithfully delineated. It was necessary to distinguish strictly the boundary of epithelium with surrounding stroma from that with lumina because the architecture of tubules in general did not coincide with that of lumina. The procedure had been repeated every two sections serially until the 50th step was reached. The drawings were then placed one upon another in series and, by looking through them, the 3-D structure of tubules and lumina were observed. Our scanning thus covered a space 350 μ thick, which was sufficient to disclose the architecture of adenoma. The results were presented in a stereogram.

As will be illustrated, the basic pattern of glands in adenoma and in well differentiated adenocarcinoma is a 3-D network. Accordingly, some variables of topology were introduced to evaluate the geometrical characteristics of these tumors.

Results

1. The architecture of adenomatous glands

The tubular adenoma presents as a sessile mucosal elevation, mostly of antrum, around which marked intestinal metaplasia predominates. Increase in number and thickness of tubules in the superficial zone is mainly responsible for this elevation, but so-called microcysts forming at the mucosal bot-

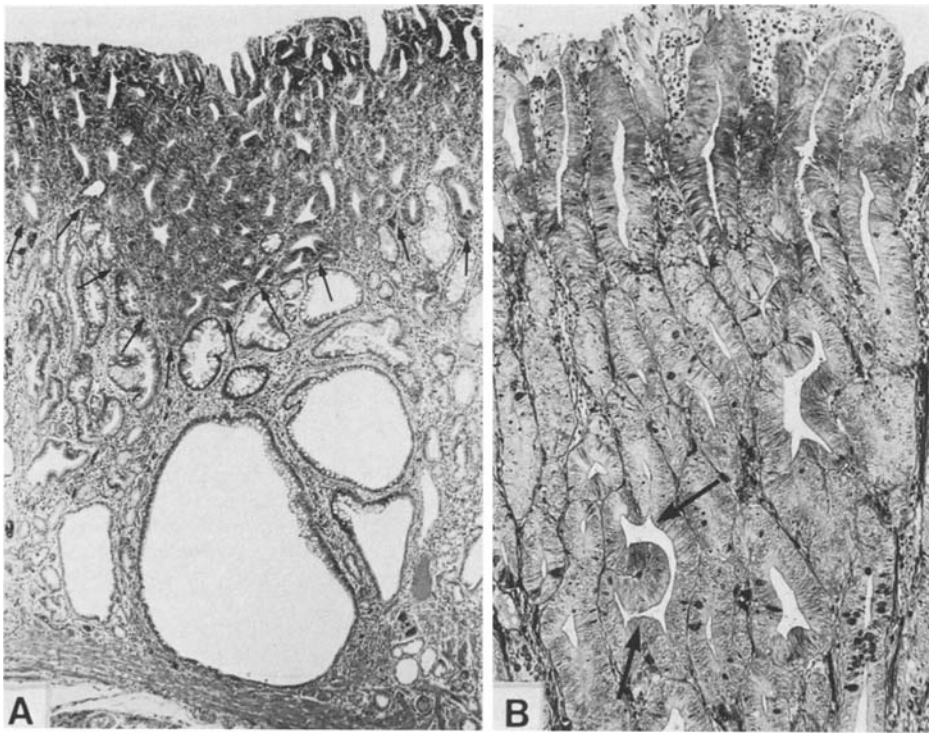


Fig. 1. A Tubular adenoma from Case 3, shown at a low magnification. A heap of atypical tubules in the upper zone are indicated by arrows. Several microcysts in the basal zone. HE-stain. ×27. **B** Higher magnification of the superficial zone of the adenoma containing atypical tubules. The arrows indicate H-patterns produced by anastomosis of adjacent tubules associated with luminal connection. Goblet or Paneth cells are dispersed in the epithelial lining. Azan-Mallory stain. ×95

tom may increase this effect (Fig 1 A). The upper tubules are lined by cells that are more or less dysplastic with elongated nuclei densely arrayed along the basal side (Fig. 1 B). Goblet or Paneth's cells are dispersed in the lining. The tubules are uniformly thick, closely packed in the lamina propria with basement membrane partially contiguous to that of neighboring tubules. Although there is no overtly malignant configuration of glands like a back-to-back pattern, deviation from normal architecture is already disclosed by H-patterns that are occasionally found and suggest intertubular connections (Fig. 1 B).

Reconstruction of the dysplastic zone in Case 3 is shown in Fig. 2. The most remarkable finding in this figure is that the atypical tubules, anastomosing with the adjacent ones at several places, are forming a network in the space (Fig. 2 A). A tubular anastomosis is confirmed by fusion of epithelial layers without intervening basement membrane. However, the lumen is also connected at some of these anastomoses, knitting the luminal system into another network. However, the meshes of the luminal network are much larger than those of the tubular network. Clearly, these net-like

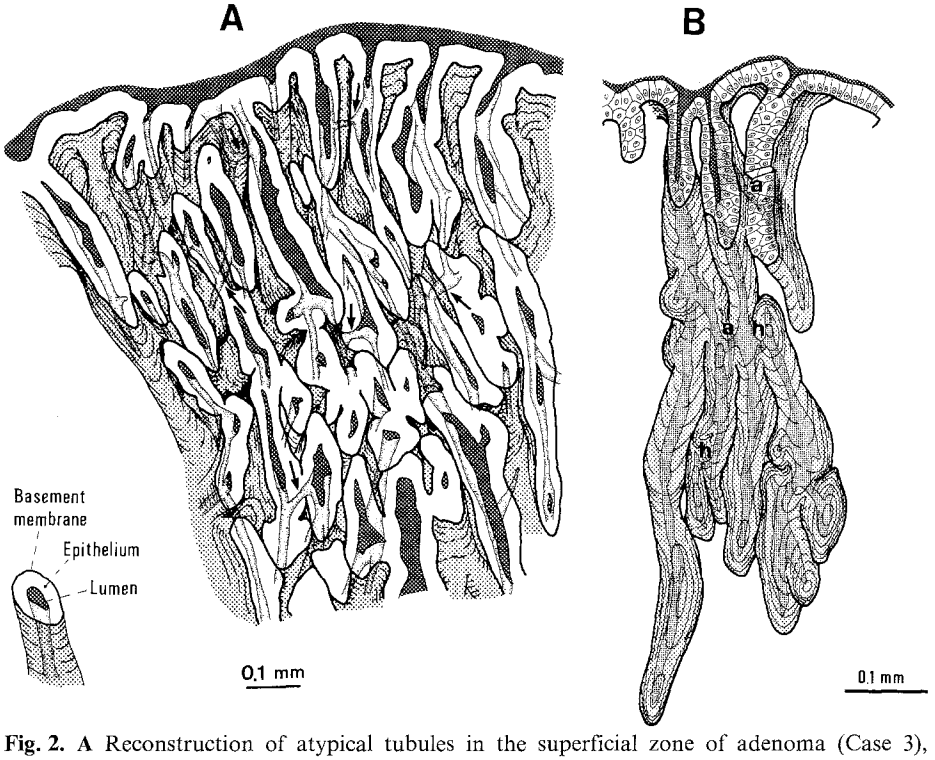


Fig. 2. **A** Reconstruction of atypical tubules in the superficial zone of adenoma (Case 3), with the lumina described with thin contour lines. Tubular anastomosis is found at several places. Indicated by arrows are the anastomoses with luminal connection. **B** Glands belonging to three neighboring pits are reconstructed. Two intertubular anastomoses showing H-pattern (a). There are however two more H-patterns produced at non-anastomotic, simply dichotomous portions (h)

structures are responsible, at least partially, for generating H-shaped tubules in section.

According to our foregoing study, a tubular network with partially continuous lumina was characteristic of well differentiated adenocarcinoma of stomach. This architecture differed essentially from the structure of ordinary gastric glands where the basic pattern was a tree that simply ramified without anastomosing among neighboring branches. In less differentiated adenocarcinoma that was the most common type of gastric cancer, the cell nests formed a network as well, but the lumina were no longer continuous and split into many separate vesicles. It was this porous structure that produced in 2-D section the so-called back-to-back pattern, a well-known feature of adenocarcinoma. The separate lumina tended to dilate and rupture apparently due to retention of secretory products.

Thus a tubular adenoma more or less mimics well differentiated adenocarcinoma not only on routine histological but on a 3-D architectural level. However, analysis of the skeleton of these tumors in quantitative-geometric terms discloses a difference: The networks contained in adenoma are far

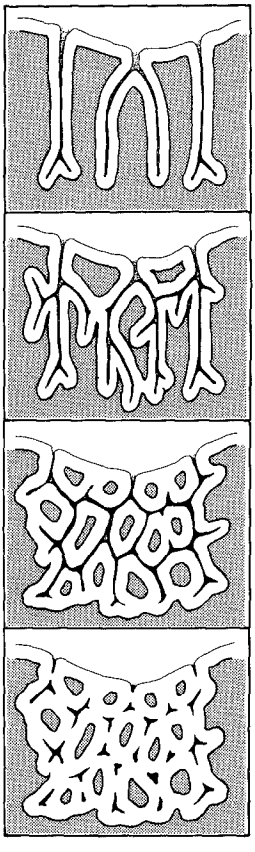
	p_0 (Number of separate parts/mm^3)		p_1 (Number of anastomosis/mm^3)	
	Tubule	Lumen	Tubule	Lumen
				
Normal	–	–	0	0
Adenoma				
Case 1	(1)	(1)	103	24
Case 2	(1)	(1)	129	29
Case 3	(1)	(1)	192	48
Adenocarcinoma well differentiated	(1)	(1)	1640	384
Adenocarcinoma moderately differentiated	(1)	439	287	0

Fig. 3. The basic architectural pattern of normal gastric glands, atypical glands in adenoma and adenocarcinomas. Shadowed are the stromal areas. Adenoma forms a 3-D network of tubules like well differentiated adenocarcinoma, though with much coarser meshes. Moderately differentiated adenocarcinoma presents as a porous structure with the lumina split into many small parts. The table formulates the values of topological parameters: p_0, the number of separate parts and p_1, that of anastomosis contained in 1 mm^3

more coarse than those in adenocarcinoma, as evidenced clearly by topological properties (Fig. 3). For instance, the number of anastomoses (p_1) of lumina ranges in adenoma from 24 to 48/mm^3 against an incomparably higher 384/mm^3 in carcinoma, showing that transformation into the cancer type is just beginning. The number of anastomosis among tubules is constantly four times that among lumina whether in adenoma or in adenocarcinoma. The other variable p_0 denotes the number of separate parts a tissue contains in 1 mm^3. For example, the porous structure of moderately differentiated adenocarcinoma is described by lumina split into 439/mm^3 vesicles.

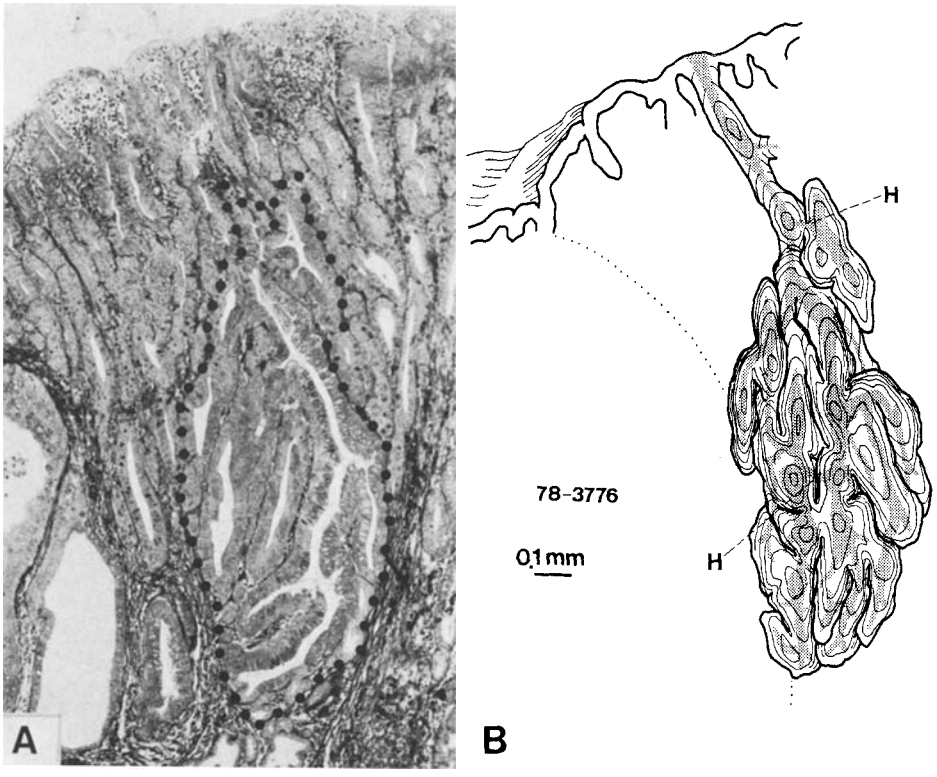


Fig. 4. A A giant arborescence from Case 3. The tubules encircled by dots belong to a giant family originating from a single pit. Azan-Mallory stain. ×42. **B** Reconstruction of the giant gland shown in the left figure. A single pit is subjected to subsequent dichotomies more than ten times. In spite of many tubular anastomoses with external glands, this family is demarcated on account of the connectivity of lumina that are united and independent of the exterior. There are several H-patterns produced in the absence of true anastomosis (*H*)

In contrast, the lumina are completely united in both adenoma and well differentiated adenocarcinoma; this is expressed in Fig. 3 as $p_0=(1)$.

2. Gland patterns: 3-D vs. 2-D

When, in sectioning an adenoma, a place of interconnection between two adjacent tubules is cut, this may appear on section as an H (X or Y)-pattern (Fig. 1B). This pattern has been variously described, for instance "bud formation of pits" (Borchard et al. 1979). Ohta (1964) paid special attention to this which he regarded as an important feature of malignant glands, distinguishing from the reverse-Y pattern of ordinary glands which ramified only toward the mucosal bottom. However, the diagnostic value of this pattern becomes compromised by its presence in benign adenomas.

On the other hand, an H found in a section of adenoma does not always correspond to a true interconnection. This is due to the formation of giant glands with extremely complicated branching (Fig. 4). In contrast to an

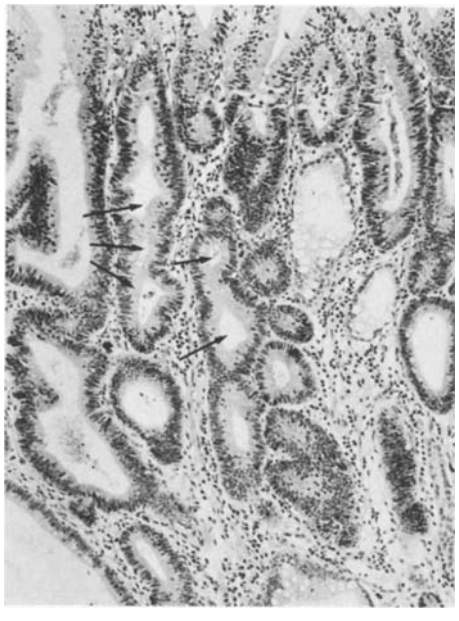


Fig. 5. "Intraglandular bridging" in atypical tubules of adenoma simulating back-to-back pattern (*arrows*). Case 2. HE-stain. ×85. This is simply due to convolution of tubules as illustrated in the right schema

ordinary pyloric gland where the tubular portion dichotomizes only once, or twice at most, a giant gland comprizes even more than ten orders of dichotomies, giving rise to a tubular conglomerate as large as 500 μ in diameter. The cells lining individual tubules vary, including epithelia of normal pyloric glands and metaplastic or dysplastic epithelia. How a giant gland produces H-patterns on section may be appreciated in Fig. 4B. When an H is recognized in a section of adenoma, it may be difficult or even impossible to determine whether it originates from a true interconnection or merely reflects complex arborization of a giant gland.

Another confusing finding in a section of adenoma is "pseudocribriform" pattern that originates from convoluted tubules. In fact, many even if not all tubules of adenoma are more or less coiled three-dimensionally, and this is probably because the tubules grow in lamina propria in which they are rather closely packed with the coexisting giant glands and microcysts (Fig. 5). This "interglandular bridging" has been interpreted as a sign of malignancy (Monaco et al. 1962), but from an architectural viewpoint it differs from a genuine back-to-back arrangement. The latter is a 2-D expression of "porous" structure in which the lumina are entirely dispersed as separate vesicles (Takahashi and Iwama: Three-dimensional morphology of gastric adenocarcinoma. Atypical glands as a basis for histopathologic diagnosis, submitted to Virchows Arch [Pathol Anat]). We have never experienced such porosity in adenoma. This anatomical difference is essential in discriminating adenoma from adenocarcinoma, on which basis the appearances of these tumors are to be evaluated. Neither ruptured glands as seen in moderately differentiated adenocarcinoma were found in adenoma.

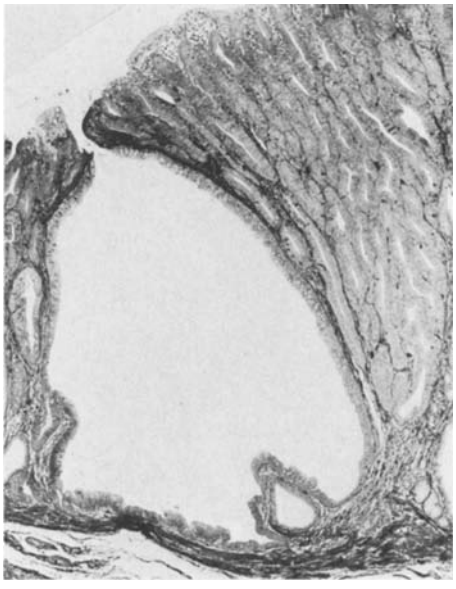


Fig. 6. A microcyst of 1.5 mm in diameter with the opening demonstrated at a step of serial sections. Azan-Mallory stain. × 33

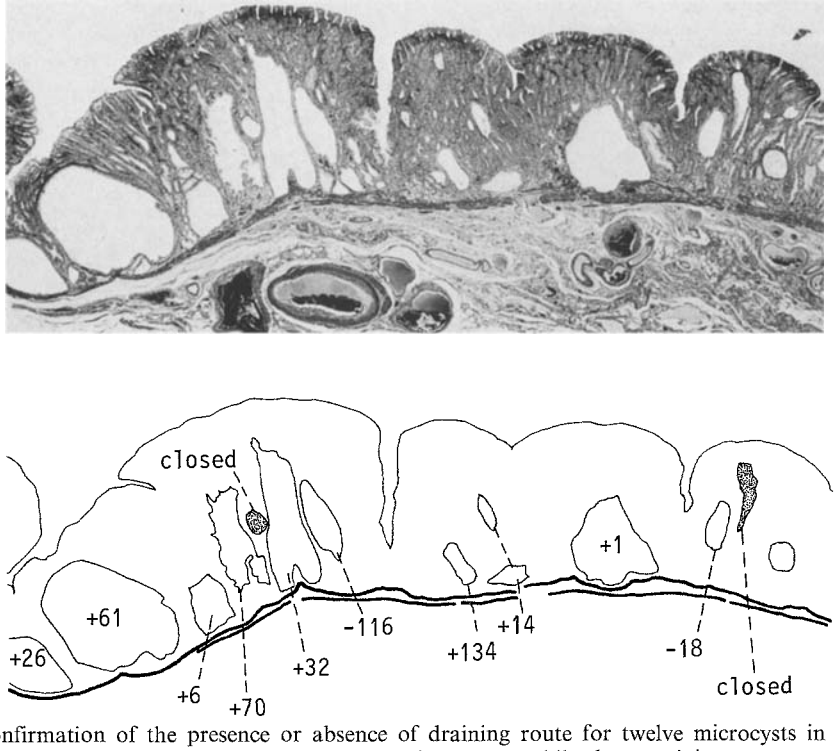


Fig. 7. Confirmation of the presence or absence of draining route for twelve microcysts in the adenoma of Case 3. Ten cysts were proved to be patent, while the remaining two were completely closed. Entered in the sketch are the step numbers of serial sections from this level to the opening of the draining system at the mucosal surface. Azan-Mallory stain. × 10.5

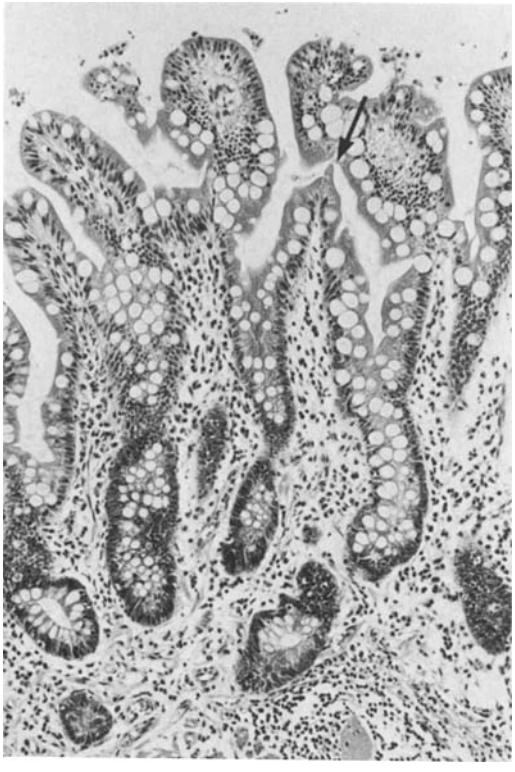


Fig. 8. Mucosa with intestinal metaplasia. The rugged contour of mucosal surface falsely suggests intertubular anastomosis as indicated by an arrow. HE-stain. ×97

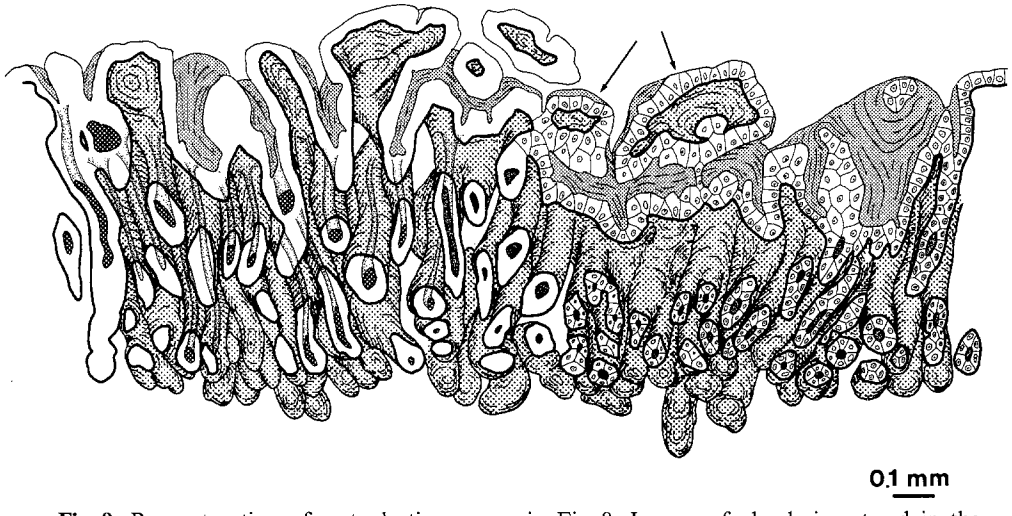


Fig. 9. Reconstruction of metaplastic mucosa in Fig. 8. Lumen of glands is entered in the left half of the figure. The surface pattern is complicated due to villous protrusions as shown by arrows. This implies a transformation of gastric into an intestinal type architecture. No intertubular anastomosis is found

3. The patency of microcysts

Usually an adenoma contains multiple dilated glands in the basal zone. Such microcysts often exceed 1 mm and are partially responsible for mucosal elevation. Controversies still remain as to whether or not these are simple retention cysts caused by obstruction of draining tubule. This has been a matter of fundamental importance in pathogenetic studies of gastric carcinoma, especially since Fujita (1981), assuming the cysts to be entirely occluded, regarded them as a closed medium favorable for proliferation of enveloped cancer cells.

In Case 3 where the microcysts were most remarkable in size and number, twelve cysts larger than 250 μ in largest diameter were traced in serial sections to examine whether there was a patent route for draining. The result shows in Figs. 6 and 7 that as many as ten out of the twelve cysts are provided with definitely patent draining tubule. In the remaining two, however, drainage is certainly absent. Tracing in serial sections reveals that the tubules from these cysts, after a short course, end at a mucous lake in upper mucosa, suggesting some destructive process preceding tubular occlusion. However, whether an occluded gland can remain long as such is unknown.

4. The architecture of metaplastic mucosa

It has been shown that intestinal metaplasia of gastric mucosa behaves as a common pathogenetic background for both adenoma and well differentiated adenocarcinoma (Morson 1955). Histologically, severe intestinal metaplasia often entails marked ruggedness of mucosal surface, which on occasion may simulate intertubular connection (Fig. 8). However, reconstruction excludes any true anastomosis among metaplastic glands, revealing nothing common to the structure of adenoma (Fig. 9). The complex surface contour of metaplastic mucosa is ascribed to multiple villous protrusions clearly shown in the stereogram. This is evidently a transformation of gastric into intestinal architecture with a two-stage structure of villi and crypts, a change macroscopically designated by Yoshii (1971) as "pseudovillus" formation. Thus the term intestinal metaplasia is justified not only by cellular features but also from an architectural point of view.

Discussion

It has been said that pathologists who are assessing malignancy in a mucosal tumor of stomach should take into account the grade of glandular disorganization as well as cellular changes. In reality this has been more said than actually done, but if well formulated, the architectural feature would serve as an important key to the discrimination between adenoma and adenocarcinoma. In order to define this morphological marker in more accurate terms, the authors recently carried out reconstruction of gastric adenocarcinomas, making clear that a series of differentiation and dedifferentiation of carcino-

ma were definable not only in conventional cytological but also in architectural aspects. In a poorly differentiated adenocarcinoma more irregular and bizarre glands were assembled than in a better differentiated one, and *vice versa*. Now, a similar approach has been applied to tubular adenomas of stomach, the malignant potential of which remains an open question. Western pathologists more readily assume potential malignancy of adenoma than Japanese, who, based on documents of many follow-up cases, tend to deny susceptibility of this tumor to malignant change (Fukuchi and Mochizuki 1982). This sort of discrepancy may be related to some regional difference, in view of the reports that the adenomas prevailing in Japan are tubular in contrast to villous variety in Western countries (Morson et al. 1980), but it is equally likely that this disagreement reflects varying standard on which the histopathological diagnosis of adenoma is made. It appears all the more mandatory to reinforce the criteria of this tumor with as many anatomical features as possible.

Reconstructions have demonstrated that adenoma shares with well differentiated adenocarcinoma a structural framework, a 3-D network for the gland, which is, however, missing in mucosa with intestinal metaplasia in spite of its close pathogenetic relationship with adenoma. But quantitative-geometrical analysis of the network classifies adenoma into a category separate from adenocarcinoma. The density of meshes is incomparably smaller as compared with that of carcinoma; the number of luminal anastomoses in adenoma ranges only from 24 to 48/mm^3 against 384/mm^3 in well differentiated adenocarcinoma. Thus it is only on a very small scale that adenoma reproduces the feature of carcinomatous glands. Moreover, in a histological section of adenomata aberrant glandular structures appear much more exaggerated than they really are. The false abnormality includes "intraglandular bridging" that emerges as a sectional pattern of convoluted tubules. It is of crucial diagnostic importance to discriminate strictly this appearance from a true back-to-back pattern which can never be demonstrated in adenomata. The back-to-back arrangement corresponds to the sectional pattern of porous tissue with dispersed vesicular lumina, a structure that is the very distinctive of common adenocarcinomas. Another confusing pattern is H-shaped tubules deriving from a normally dichotomizing gland. This again corresponds to distorted and convoluted tubules that proliferate while being squeezed in a narrow space of mucosal zone. The transformation further advances when bulging lesions like giant glands and microcysts form, applying pressure on the coexisting tubules. Thus an adenoma, with qualities basically similar to but far less prominent than well differentiated adenocarcinoma, is nothing more than its miniature.

When epithelial dysplasia is severe enough in an adenoma-like lesion, discussion may arise about whether or not a diagnosis of adenocarcinoma in situ is justifiable. The above 3-D morphology clearly illustrates this point. Theoretically, in situ adenocarcinoma should be defined as a state in which the epithelial lining of glands has been replaced by cancer cells while the glands maintain the preformed architecture. However, an as yet benign adenoma already harbors altered glandular architecture. When malignant

transformation follows this, disorganization of glands advances further and there can be no room for an in situ adenocarcinoma to develop during the transition of mucosal change from adenoma to adenocarcinoma. We agree with Mochizuki (1971), Morson and Dawson (1979) and Kraus and Cain (1979) that it is not feasible to categorize histologically in situ adenocarcinoma of stomach.

Our interest is now concentrated on the general rule according to which the glandular pattern changes when a precancerous lesion evolves into adenocarcinoma. Ohuchi, one of our colleagues, recently demonstrated a transition of structure in intraductal tumors of breast, showing that a continuous luminal network in papilloma or papillomatosis became separated into porous lumina as carcinoma developed in these lesions (Ohuchi N, Tezuka F, Takahashi T, Abe R: Atypical glandular pattern in intraductal carcinoma and papilloma of the breast based on 3-D reconstruction studies, submitted to J Clin Pathol). It is very interesting that in either gastric or mammary tumors, it is the tubular network that characterizes the precancerous stage and precedes overt carcinoma. The extent of this change does not appear very strictly demarcated since, for instance, an adenocarcinoma of stomach has the same skeleton when the differentiation is extremely high. A network is an intermediate state not only in the clinical sense that it characterizes most borderline malignant cases but also geometrically; it comes between the dichotomous tree of normal glands and the porous state of common adenocarcinoma. Based on these considerations it may be justified to assume that adenoma is a true neoplasm. Equally likely, the 3-D architecture of a glandular tumour is a true reflection of its biological behavior and serves as a morphological marker of malignancy.

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