Histopathologic Studies of Gastric Ulcer-Carcinoma

I. On the Origin of Gastric Ulcer-Carcinoma

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Making histologic examination of many gastrectomy specimens of gastric carcinoma and ulcer kept in our clinic, I found 86 cases of ulcer-carcinoma, including 18 cases in which the ulcer base was free of carcinoma. Close examination of these 18 cases, which had been found to meet the two critical criteria for the diagnosis of ulcer-carcinoma as set up by Hauser,1) presented some interesting information as to the development of carcinoma from ulcer, as will be reported below.

Results

Macroscopic observations. The lesions, which measured from 0.5 x 0.5 cm. to 4 x 4 cm., were found in the corpus ventriculi in 9 of the 18 cases, and at the pars pylorica in the remaining 9 cases. A remarkable radiating fold of the gastric mucosa toward the ulcer was observed in a part of the ulcer in 3 cases, and over the entire margin in the remaining 15 cases. Cross sections of all the specimens revealed that the muscular coat was completely destroyed, their free ends characteristically bent upward into the ulcer margin, and the base of the ulcer was made up of callous omentum tissue.

Microscopic observations. In 16 of the 18 cases, the entire ulcer was divided into 10 to 45 serial blocks; and in 2 cases a great part of the ulcer was divided into 10 to 15 blocks. These blocks were fixed and embedded in paraffin. When necessary, serial sections were made, and stained with hematoxylin and cosin and with Van Gieson’s stain. Mallory’s connective-tissue stain, mucicarmine, or the Bielschowsky silver method was also used on some sections.

The 18 cases were classified into two groups according to the depth of carcinomatous infiltration at the ulcer margin: (1) the first grade group (11 cases), in which the infiltration did not beyond the mucous membrane, and (2) the second grade group (7 cases), in which the in-
filtration attained to the muscular coat.

(a) The first grade group of ulcer-carcinoma. Case 1 was a callous ulcer in the corpus ventriculi (Fig. 1). A comparatively high extent of

Fig. 1. Ulcer-carcinoma specimen (Case 1) cut open on the greater curvature. The portions surrounded by broken lines represent the areas of early malignant degeneration.

atypical epithelial proliferation was seen almost all along the margin of the ulcer, and at a place of the margin a single layer of regenerative epithelium was found to extend from the margin of the ulcer toward its base (Fig. 2). At three places (A, B, C in Fig. 1) of the ulcer margin, however,

Fig. 2. Part of atypically proliferated epithelium. The arrows point to a layer of regenerative epithelium covering the base of the ulcer.

there were found solitary foci of cancer (i.e., an epithelial overgrowth more advanced than atypical epithelial proliferation). At A, proper gastric glands totally disappeared and were replaced by a highly atypical glandular tissue consisting of acini of various sizes and shapes; the basement membrane of these acini could not be perceived even in silver-
stained sections. The arrangement of cells of the neoplastic glands was irregular and close; the cells were mostly tall cylindrical and partly cuboidal; their nuclei were hyperchromatic, of irregular shape, of various sizes, and showed mitotic figures scatteringly. These proliferating cells invaded the submucous coat adjoining the ulcer margin to form acini of various sizes and shapes (Fig. 3). B and C were adenomatous cancer foci; their glandlike structures were arranged more irregularly than those of A, partly forming solid epithelial cords. However, these foci were localized, there being found no carcinomatous invasion of the submucous coat (Fig. 4). A gradual transition was observed between these three
cancer foci and the regenerative epithelium of atypical growth.

The mode of development of the cancer focus in the remaining 10 cases belonging to the first grade group is diagrammatically shown in Fig. 5. In cases 2 and 3, atypical overgrowth of regenerative epithelium was seen all along the ulcer margin; areas of early malignant degeneration were also noticed at two or three places. In case 2 there were seen, in addition, a small adenomatous cancer focus, which was located 2 cm. apart from the ulcer margin and localized at the mucous membrane.

In cases 4 and 5, atypical epithelial proliferation was found in a part of the ulcer margin; areas of early malignant degeneration were also noted at one to three places of the margin. Though they were adenocarcinomas on the whole, the cells were smaller than those in the above three cases and showed a strong tendency to form a solid clump of cells. Partly, carcinomatous infiltration of the submucosa was also observed (Fig. 6). In case 5, a small area of adenocarcinoma was found in addition, 2.5 cm. apart from the ulcer margin. This focus was localized at the mucous membrane on the whole, but carcinomatous invasion of the submucosa was revealed, though only partly.

In case 6, the ulcer was narrow and long, and beared 8 distinct areas
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of carcinoma solidum (from $550 \times 1000 \mu$ to $1.0 \times 1.3$ cm.): 2 comparatively large and 6 small cancer foci. All these were still localized at superficial layers of the mucous membrane, and atypical overgrowth of regenerative epithelium was also seen around them (Fig. 7).

Fig. 6

Fig. 7

Fig. 6. Area of early malignant degeneration (Case 5). The arrow indicates infiltration of the submucosa.

Fig. 7. Cancer focus at the ulcer margin (Case 6). A, regenerative epithelium covering the base of the ulcer; B, base of the ulcer. The portion surrounded by arrows represents the focus of carcinoma solidum.

In cases 7 and 8, 8 cancer foci were observed: 7 foci of carcinoma solidum as in case 6 and 1 focus of tall cylindrical-celled adenocarcinoma (C in case 8, Fig. 8). Many of them were superficial and localized carcinomas of the mucous membrane, while submucous infiltration by cancer cells was noticed at D of case 7 and at C of case 8.

In case 9, which has already been reported in detail by Abe and others, there were found at the ulcer margin 2 solitary adenomatous cancer foci localized between the superficial layer of the mucous membrane and the submucosa, together with 3 solitary precancerous foci.

In case 10, a carcinoma solidum was found almost completely around the ulcer margin, and in case 11 a adenocarcinoma was seen completely around the margin. In case 10, proper gastric glands still remained at the places, a, b, c, and d, where cancer cells existed only interstitially (Fig. 9). This produced the appearance that independent cancer foci had fused at the four places. The cancer foci were mostly confined to the superficial layer; submucous infiltration, however, was noted at the
places A and B in case 10.

(b) The second grade group of ulcer-carcinoma. The mode of development of carcinoma in 7 cases belonging to the second grade group is shown diagramatically in Fig. 10. Of these 7 cases, 3 (cases 12 to 14) have already been reported in detail by Abe and others.\(^2\)\(^3\) In case 12,
there were found 3 isolated foci: A of adenocarcinoma with cancerous infiltration reaching the muscular layers, and B and C of carcinoma solidum well localized at the mucous membrane of the ulcer margin.

In cases 13 and 14, colloid carcinoma was seen completely around the ulcer margin except a small portion. In addition, a solitary small carcinoma solidum was found in case 13, localized at the mucous membrane and a little apart from the ulcer margin; in case 14, there existed 3 solitary precancerous foci.

In case 15, there were found a carcinoma solidum completely around the ulcer margin and a solitary adenocarcinoma adjoining the pyloric ring and consisting of tall cylindrical cells; part of cancer cells were found to have penetrated the submucosa, attaining even to the muscular layers.

In cases 16 to 18, diffusely infiltrating carcinoma solidum was seen completely around the ulcer margin as in case 15, but the base of the ulcer was entirely free of cancer.

**DISCUSSION**

Hauser stated that cancerous degeneration in gastric ulcer originates in atypical epithelial proliferation of glandular tissue at the ulcer margin. Moszkowicz sought for the cause of such an atypical proliferation in the reparative function of the epithelium of the gastric foveola. Recently Kuru has reported that ulcer-carcinoma develops in the mucous membrane regenerated for repairing the ulcerated defect. Murakami has reported those cases in which glandular and solid cancers developed from regenerative epithelium.

All the areas of early malignant degeneration as found in cases 1 to 8 of the 18 cases in the present study resulted from changes that had occurred in a part of the atypically proliferated mucous membrane at the ulcer margin. Furthermore, areas of early malignant degeneration were clearly recognized in a field of atypical proliferation of regenerative epithelium in cases 1 to 3, and 6. In view of a gradual transition seen between cancer tissue and regenerative mucous membrane in 3 of the above cases, it may be concluded that these areas of early malignant degeneration originated in the regenerative epithelium. From these findings it may be inferred that atypically proliferating cells appear in process of the epithelial regeneration in ulcer and some of them make cancerous change.

On close examination of early gastric cancers as to their development, Konjetzny, Ewing, and others found many early superficial carcinomas over a comparatively large area of the mucous membrane, and asserted that gastric cancer develops multicentrically. Recently, Collins and Gall have supported this conception of multicentric development by
their findings that even with cases of established invasive carcinoma close examination in the neighborhood of the main cancer focus revealed the presence of microscopic pre-invasive carcinoma there, and that even the main cancer focus was often composed of several cancers of different histologic types. In the case of ulcer-carcinoma also, Hauser,1) Stoerk,11) and others stated that cancerous change at the ulcer margin may occur multicentrically at several places of the ulcer margin. Klein,12) Suzuki,13) Murakami6)7) and Ayabe14) have reported those cases in which cancer developed multicentrically at or around the ulcer margin.

In 7 of the 18 cases (cases 1 to 3, and 5 to 8) in the present study, a total of 29 solitary areas of early malignant degeneration or of small cancer (2 to 8 areas in a case) were found at or apart from the ulcer margin, in 4 cases (cases 9, 12 to 13, and 15), a total of 5 solitary small cancer foci were found (1 to 2 areas in a case), in addition to the main cancer foci occupying a large area at the ulcer margin. The solitude of each of these 34 small “solitary” cancer foci was ascertained by examination of serial blocks of the entire ulcer and of serial sections of part of the ulcer. Twenty-five of these 34 cancer foci were completely restricted to the superficial layer of the mucous membrane; in 8 cancer foci, cancer cells penetrated the muscularis mucosae and reached the underlying submucosa; and only in the remaining 1 focus, cancer cells were found to infiltrate as far as the muscular layers. In each of cases 9 and 14, 3 precancerous foci, independent of cancer foci at the ulcer margin, were also present at the mucous membrane apart from the latter foci. It is also to be noted that solitary cancer foci as found at the ulcer margin or at the mucous membrane apart from it (cases 8, 12, 13, 15) were clearly of different histologic types.

From what has been stated above it may be taken that multiple development of solitary cancer foci has been demonstrated in 11 of the 18 cases. In addition, the following facts are also suggestive of this multiple development: Some of these solitary cancer foci were of different histologic types, and a few of them were at different stages as judged by the extent of infiltration of deeper layers. In 2 of the 11 cases belonging to the first grade group (where the cancer foci were superficial) and in 6 of the 7 cases of the second grade group (where cancerous infiltration reached the muscular layers) cancer cells were found to have extended completely or almost completely around the ulcer margin. Thus, there was no conclusive evidence of the multicentric development in these cases. However, in 1 case (case 10) of the first grade group pictures indicative of a fusion of independently developed cancer foci were seen; and in 3 cases (cases 13 to 15) there were found small cancerous or precancerous foci, apart from the cancer foci com-
pletely around the ulcer margin and localized at the mucous membrane. From these findings and the incidence of not a few cases demonstrating multicentric development of cancer foci as stated above it may be inferred that even in cases in which a cancer focus completely surrounded the ulcer margin, canceration had originated multicentrically, and independently formed cancer foci fused by their progressive enlargement, with one another.

**Summary**

1. Examination was made of 18 cases with ulcer-carcinoma in early stages by the serial section method.

2. Ulcer-carcinoma seems to originate from regenerative epithelium of atypical proliferation.

3. In 11 of the 18 cases with early ulcer-carcinoma, multicentric development of cancer foci has been demonstrated at the ulcer margin or in the mucous membrane apart from the ulcer margin. In the remaining 6 cases, except 1 case in which a small cancer focus was found in a very small portion of the ulcer margin, cancer foci extended to surround the ulcer margin completely or almost completely, being thus suggestive of the fusion of multicentrically developed cancer foci.

**References**

3) Abe, Majima & Kurakake, Igaku (Jap.), 1952, 8, 280.
6) Murakami, ibid., 1951, 51, 651.
14) Ayabe, Igaku (Jap.), 1949, 6, 268.