Comparative Studies on Dysplasia of Esophageal Epithelium in Four Prefectures of Japan (Miyagi, Nara, Wakayama and Aomori) with Reference to Risk of Carcinoma

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MUKADA, T., SATO, E. and SASANO, N. Comparative Studies on Dysplasia of Esophageal Epithelium in Four Prefectures of Japan (Miyagi, Nara, Wakayama and Aomori) with Reference to Risk of Carcinoma. Tohoku J. exp. Med., 119 (1), 51-63 — Distal two-thirds of the esophagus without macroscopically detectable malignant lesions from a total of 248 autopsy cases were examined for epithelial dysplasia on histological sections from serial blocks. The autopsy specimens had been obtained from Miyagi, Nara and Wakayama prefectures known for high incidence of esophageal carcinoma in Japan, and Aomori prefecture where the incidence of the disease is low. Epithelial dysplasia was classified into mild, moderate, and severe including carcinoma in situ according to the grade of epithelial atypism. Of 248 cases 91 (36.7%) had epithelial dysplasia and 30 (12.1%) had moderate and severe dysplasia. In one of the cases of severe dysplasia, in situ carcinoma was diagnosed. Lesions of dysplasia of the resected specimen were displayed in a diagram for the distribution of the abnormal epithelium. Cases of higher grade dysplasia tended more extensive in area and were slightly dominant in the distal third of the esophagus. Possible relationships of dysplasia with long-standing irritation to the esophagus and with precancerous lesions were discussed.

Esophageal carcinoma is one of the commonest malignancies in Japan and its mortality rate of population level is high compared with other countries in the world. High risk to esophageal carcinoma might be caused by some environmental factors (Craver 1932; Wynder and Mabuchi 1973; Segi 1975; Kamon and Hirayama 1975). According to Segi and Kurihara (1974), the mortality rate of esophageal carcinoma differs among 46 prefectures in Japan. Questions will be aroused whether or not the incidence of precancerous lesions of the esophagus differs between prefectures of high and low risk to esophageal carcinoma. The purpose of this study is to evaluate dysplasia of the esophageal epithelium, a proliferative lesion of atypical cells possibly precancerous, through histological observation and to

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compare its incidence between prefectures of high risk to esophageal carcinoma (Miyagi, Nara and Wakayama) and of low risk (Aomori).

**Materials and Methods**

Materials used were the esophagus of 248 autopsy cases over 40 years of age collected from Miyagi, Nara, Wakayama and Aomori prefectures (Table 1). Cases of macroscopically detectable lesions of carcinoma were excluded. Epithelial lesions of small white patches (leukoplakia) and of esophagitis with erosions were not rare and they were included in the examination.

Distal two-thirds or more of the esophagus were transversely sectioned into 5 mm thick serial slices and embedded in paraffin (Fig. 1). Histological sections, prepared from the oral surface of each block, were stained with hematoxylin and eosin and if necessary with Gomori’s silver impregnation. Histological changes of the epithelium in serial blocks were presented in a diagram for indicating the distribution of lesions of individual cases. For the control study, 10 normal esophagi of autopsy cases under 30 years of age were examined in the same way.

**Table 1. Materials**

<table>
<thead>
<tr>
<th>Age groups</th>
<th>Miyagi</th>
<th>Nara</th>
<th>Wakayama</th>
<th>Aomori</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>M</td>
<td>F</td>
<td>M</td>
<td>F</td>
<td>M</td>
</tr>
<tr>
<td>40-49</td>
<td>3</td>
<td>3</td>
<td>6</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>50-59</td>
<td>10</td>
<td>7</td>
<td>17</td>
<td>6</td>
<td>12</td>
</tr>
<tr>
<td>60-69</td>
<td>21</td>
<td>16</td>
<td>37</td>
<td>8</td>
<td>7</td>
</tr>
<tr>
<td>70-79</td>
<td>10</td>
<td>9</td>
<td>19</td>
<td>8</td>
<td>10</td>
</tr>
<tr>
<td>80+</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>-</td>
<td>4</td>
</tr>
<tr>
<td>Total</td>
<td>46</td>
<td>38</td>
<td>84</td>
<td>24</td>
<td>32</td>
</tr>
</tbody>
</table>

Fig. 1. Material after sectioning. Arrows indicate the level of bifurcation (left) and of esophagogastric junction (right).

**Results**

**Evaluation of dysplasia**

The normal epithelium showed regularly arranged squamous cell layers
measuring 200–500 μm in thickness. Tangential basal cell linings were clearly distinguishable from the upper prickle cells. Mitotic figures were rarely observed and they were limited in the basal and parabasal layers. Rete ridges were uniform in shape and size (Fig. 2). Leukoplakia, macroscopically manifesting small white patch, was not rarely observed as a lesion of well circumscribed epithelial hyperplasia without cellular atypism. Epithelial abnormalities as histopathological deviations from the normal stratified squamous epithelium toward carcinoma in situ were designated as “dysplasia”. The lesions were categorized as “mild”, “moderate” and “severe” depending on the degree of cellular and structural atypism.

In mild dysplasia, the epithelium tended to increase in thickness. Slightly atypical cells with somewhat larger and hyperchromatic nuclei were found only in basal 1/2 or less of the epithelium preserving cellular alignment (Fig. 3).

In moderate dysplasia, atypical cells associated with occasional mitotic figures were prominent in basal 2/3 or less of the epithelium. Slight disarrangement of epithelial cells was observed with or without thickening of the entire epithelium. Differentiation between basal and parabasal layers was often impossible (Figs. 4 and 5).

In severe dysplasia, disarrangement of epithelial cells was remarkable besides moderate cellular atypism with nuclear pleomorphism observable in basal 2/3 or more of the epithelium (Figs. 6 and 7).

In carcinoma in situ, cellular atypism was far extensive and every finding was compatible with cancer except for the absence of invasive growth. A careful
Fig. 3. Mild dysplasia. M-120. (hematoxylin and eosin stain, × 100).
Cellular atypism progresses toward the right side.

Fig. 4. Moderate dysplasia. A-2909. (hematoxylin and eosin stain, × 45, × 100).
Marked downward growth of the epithelium.

observation of our series, however, demonstrated evidence of an early stage of invasion across the basement membrane (Figs. 8 and 9).

In the following observation “higher grade dysplasia” includes moderate and
severe dysplasia and carcinoma in situ.

*Incidence of esophageal dysplasia*

In our series, a total of 91 of the 248 cases showed dysplasia (36.7%). The
Fig. 7. Severe dysplasia. N-2965. (hematoxylin and eosin stain, × 100). Atypical cells with numerous mitotic figures replace almost entire thickness of the epithelium.

Fig. 8. Carcinoma in situ. M-105. (hematoxylin and eosin stain, × 100). Marked nuclear dispolarity is seen. Two different cell types coexist side by side, prickle cells in the left half of the picture and basal cells in the other.

The incidences of the lesion in male and female were practically equal being 53/147 (36.1%) in male and 38/101 (37.6%) in female. The incidences of the lesion in 4 prefectures did not differ greatly, being 26/84 (31.0%) in Miyagi, 23/56 (41.1%)
in Nara, 18/46 (39.1%) in Wakayama and 24/62 (38.7%) in Aomori.

Higher grade dysplasia was limited in number with an incidence of 30/248 (12.1 %), one-third of all grade dysplasia, through 4 prefectures (Table 2). Miyagi and Nara slightly exceeded the others in incidence. The incidence in female 14/101 (13.9%) exceeded that in male 16/147 (10.9%).

Location and extent of dysplasia

Of 91 cases of dysplasia, 22 (24%) involved the middle third, 36 (40%) the distal third and 33 (36%) involved both. In regard to higher grade dysplasia, 11 (37%) involved the middle third, 17 (57%) the distal third and 2 (6%) involved both.

Diagrams for the distribution of the abnormal epithelium showed that lesions of higher grade dysplasia were unexceptionally associated with those of less severe grade. In the cases of lesser extent, lesions of dysplasia of any grade were usually small and multicentric (Fig. 10).

The extent of dysplasia quantitatively estimated from the diagram served for the calculation of dysplastic area in percent of the total area of the esophageal epithelium examined. In the cases of extensive involvement (over 70%), lesions of higher grade dysplasia appeared more frequently than in the less extensive cases (Fig. 11). This phenomenon was particularly evident in older age groups (Fig. 12). Skip-wise lesions, composed of two or more isolated foci of dysplasia with a distance of 0.5 cm or more, were observed in 44 of 91 cases (48.4%).
TABLE 2. Incidences of

<table>
<thead>
<tr>
<th>Age groups</th>
<th>Miyagi M</th>
<th>F</th>
<th>Total</th>
<th>Nara M</th>
<th>F</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>40-49</td>
<td>0.00%</td>
<td>33.33%</td>
<td>16.66%</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>(0/3)</td>
<td>(1/3)</td>
<td>(1/6)</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>50-59</td>
<td>10.00%</td>
<td>0.00%</td>
<td>5.88%</td>
<td>16.66%</td>
<td>25.00%</td>
<td>22.22%</td>
</tr>
<tr>
<td></td>
<td>(1/10)</td>
<td>(0/7)</td>
<td>(1/17)</td>
<td>(1/6)</td>
<td>(3/12)</td>
<td>(4/18)</td>
</tr>
<tr>
<td>60-69</td>
<td>0.00%</td>
<td>6.25%</td>
<td>2.70%</td>
<td>0.00%</td>
<td>14.28%</td>
<td>6.66%</td>
</tr>
<tr>
<td></td>
<td>(0/21)</td>
<td>(1/16)</td>
<td>(1/37)</td>
<td>(0/8)</td>
<td>(1/7)</td>
<td>(1/15)</td>
</tr>
<tr>
<td>70-79</td>
<td>20.00%</td>
<td>33.33%</td>
<td>26.31%</td>
<td>12.50%</td>
<td>20.00%</td>
<td>16.66%</td>
</tr>
<tr>
<td>80+</td>
<td>50.00%</td>
<td>66.66%</td>
<td>60.00%</td>
<td>0.00%</td>
<td>0.00%</td>
<td>0.00%</td>
</tr>
<tr>
<td></td>
<td>(1/2)</td>
<td>(2/3)</td>
<td>(3/5)</td>
<td>(0/4)</td>
<td>(0/2)</td>
<td>(0/6)</td>
</tr>
<tr>
<td>Total</td>
<td>8.69%</td>
<td>18.42%</td>
<td>13.09%</td>
<td>8.33%</td>
<td>18.75%</td>
<td>14.28%</td>
</tr>
</tbody>
</table>

* Including dysplasia of moderate and severe and carcinoma in situ.

Fig. 10. Distribution of dysplastic lesions in individual cases. Cases are of Miyagi prefecture (M), Nara (N) and of Aomori (A).
Dysplasia: ■ mild; □ moderate; ■ severe; □ ca. in situ; → level of bifurcation.

Relationships between dysplasia and other changes of esophagus

Chronic esophagitis was demonstrated in 7.7% (19/248 cases). Dysplasia was associated with chronic esophagitis at a significant level p<0.01 in Miyagi, and p<0.05 in total 4 prefectures (Table 3).

Ductal ectasia of the esophageal gland, even cystic in advanced cases, was seen in 25.8% (64/248 cases). In Nara prefecture, dysplasia was frequently associated with ductal ectasia (70%, 14/20 cases) at a significant level p<0.001.
Higher grade dysplasia

Wakayama | Aomori | Total
---|---|---
M | F | Total | M | F | Total | M | F | Total
---|---|---|---|---|---|---|---|---
--- | --- | --- | 100% | 100% | 0.00% | 50.00% | 28.57%
--- | --- | --- | (1/1) | (1/1) | (0/3) | (2/4) | (2/7)
0.00 | 0.00 | 0.00 | 15.38 | 0.00 | 11.11 | 10.52 | 10.71 | 10.60
(0/2) | (0/4) | (0/13) | (2/13) | (0/5) | (2/18) | (4/38) | (3/28) | (7/66)
25.00 | 0.00 | 17.64 | 20.00 | 0.00 | 13.33 | 9.80 | 6.06 | 8.33
(3/12) | (0/5) | (3/17) | (2/10) | (0/5) | (2/15) | (5/51) | (2/33) | (7/84)
12.50 | 0.00 | 8.33 | 11.76 | 0.00 | 9.09 | 13.95 | 17.85 | 15.49
(1/8) | (0/4) | (1/12) | (2/17) | (0/5) | (2/22) | (6/43) | (5/28) | (11/71)
0.00 | - | 0.00 | 0.00 | 0.00 | 0.00 | 8.33 | 25.00 | 15.00
(0/4) | (0/6) | (0/4) | (0/2) | (0/6) | (1/12) | (2/8) | (3/20)
12.12 | 0.00 | 8.69 | 13.63 | 5.55 | 11.29 | 10.88 | 13.86 | 13.09

Fig. 11. The incidence of higher grade dysplasia by extent of dysplasia. The higher grade dysplasia includes moderate and severe dysplasias and carcinoma in situ. The extent of dysplasia shows dysplastic area in percent of the total area of the esophageal epithelium examined. The more extensive the dysplastic lesion is, the more frequently it is accompanied by higher grade dysplasia.

Hyperplasia of the duct epithelium occasionally associated with metaplasia was seen in 12.9% (32/248 cases) and it was particularly accompanied by dysplasia at significant levels in Miyagi, Nara and in total 4 prefectures, p<0.05, p<0.02, and p<0.05, respectively (Table 4).

Regenerated epithelium, though it rarely showed dysplastic changes, was observed in 8.5% (21/248 cases). Dysplasia was frequently observed in cases having epithelial regeneration at significant levels, 67% (4/6) in Miyagi, 83% (5/6 cases) in Nara and 57% (12/21 cases) in total, p<0.05 respectively (Table 5).

Leukoplakia was identified in 50.4% (125/248 cases). There was no tendency that the incidence of dysplasia was high in the cases with leukoplakia compared with the cases without this lesion.
Fig. 12. Extent of dysplasia in various age groups. Differences between means of higher grade dysplasia and mild dysplasia are statistically significant, \( p<0.05 \) in groups of 50~59 and 60~69, and \( p<0.001 \) in those of 70~79 and 80 and over by \( t \)-test.

<table>
<thead>
<tr>
<th>Age groups (years)</th>
<th>40~</th>
<th>50~</th>
<th>60~</th>
<th>70~</th>
<th>80~</th>
</tr>
</thead>
<tbody>
<tr>
<td>Extent of dysplasia (%)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

\( *, \) higher grade dysplasia; \( \ast, \) mild dysplasia; ---, mean of higher grade dysplasia; ---, mean of mild dysplasia; ----, mean of all cases in each age group.

**Table 3. Dysplasia associated with chronic esophagitis**

<table>
<thead>
<tr>
<th>Miyagi</th>
<th>Nara</th>
<th>Wakayama</th>
<th>Aomori</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic esophagitis</td>
<td>( 100%^* )</td>
<td>( 60.00% )</td>
<td>( 50.00% )</td>
<td>( 33.33% )</td>
</tr>
<tr>
<td>( (+) )</td>
<td>( (3/3) )</td>
<td>( (3/5) )</td>
<td>( (4/8) )</td>
<td>( (1/3) )</td>
</tr>
<tr>
<td>( (-) )</td>
<td>( 28.39%^* )</td>
<td>( 39.21% )</td>
<td>( 36.84% )</td>
<td>( 38.98% )</td>
</tr>
<tr>
<td>( (23/81) )</td>
<td>( (20/51) )</td>
<td>( (14/38) )</td>
<td>( (23/59) )</td>
<td>( (80/229) )</td>
</tr>
</tbody>
</table>

* \( p<0.01 \), † \( p<0.005 \).

**Table 4. Dysplasia associated with duct epithelial hyperplasia of esophageal gland**

<table>
<thead>
<tr>
<th>Miyagi</th>
<th>Nara</th>
<th>Wakayama</th>
<th>Aomori</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperplasia</td>
<td>( 62.50%^* )</td>
<td>( 77.77%^\dagger )</td>
<td>( 16.66% )</td>
<td>( 44.44% )</td>
</tr>
<tr>
<td>( (+) )</td>
<td>( (5/8) )</td>
<td>( (7/9) )</td>
<td>( (1/6) )</td>
<td>( (4/9) )</td>
</tr>
<tr>
<td>( (-) )</td>
<td>( 27.63%^* )</td>
<td>( 34.94%^\dagger )</td>
<td>( 42.50% )</td>
<td>( 37.73% )</td>
</tr>
<tr>
<td>( (21/76) )</td>
<td>( (16/47) )</td>
<td>( (17/40) )</td>
<td>( (20/53) )</td>
<td>( (74/216) )</td>
</tr>
</tbody>
</table>

*; † \( p<0.05 \), † † \( p<0.02 \).

**DISCUSSION**

The esophagus is still behind the uterine cervix and gastrointestinal tracts in establishment of the notion of precancerous lesion because of several unfavorable conditions.
TABLE 5. Dysplasia associated with the presence of regenerated epithelium*

<table>
<thead>
<tr>
<th>Regeneration</th>
<th>Miyagi</th>
<th>Nara</th>
<th>Wakayama</th>
<th>Aomori</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>(+)</td>
<td>66.67%†</td>
<td>68.33%‡</td>
<td>60.00%</td>
<td>0.00%</td>
<td>57.14%§</td>
</tr>
<tr>
<td></td>
<td>(4/6)</td>
<td>(5/6)</td>
<td>(3/5)</td>
<td>(0/4)</td>
<td>(12/21)</td>
</tr>
<tr>
<td>(−)</td>
<td>28.20%†</td>
<td>36.00%‡</td>
<td>36.58%</td>
<td>41.37%</td>
<td>43.49%§</td>
</tr>
<tr>
<td></td>
<td>(22/78)</td>
<td>(19/53)</td>
<td>(15/41)</td>
<td>(24/59)</td>
<td>(79/227)</td>
</tr>
</tbody>
</table>

* Regenerated epithelium, per se, rarely showed dysplasia.
†, ‡, § p<0.05.

In recent years, attention has been paid to “early carcinoma” of the esophagus limitedly involving mucosal and submucosal layers and some dozens of cases have been reported to date (Nabeya 1970; Nabeya et al. 1974). On the other hand, “carcinoma in situ” or “intraepithelial carcinoma” of the esophagus appeared in the literature only as a concomitant lesion with carcinoma (Sato 1955; O’Gara and Horn 1955; Suckow et al. 1962; Akiyama et al. 1969). Ushigome et al. (1967) reported a case of carcinoma in situ associated with widely spread dysplasia of the epithelium. Arimori et al. (1971) mentioned about a dysplastic lesion in a case report of early carcinoma. As far as we know, mass survey of precancerous lesions of the esophagus per se could not be obtained except through the study of exfoliative cytology (The Coordinating Groups for Research of Esophageal Carcinoma, Honan Province and Chinese Academy of Medical Science 1975). It is one of our interests whether or not dysplasia of the esophageal epithelium is fully qualified as a precancerous lesion. The present investigation revealed that dysplasia of the esophageal mucosa progressed in severity pacing with its extension. And further, the evil extremity in the spectrum of atypism was compatible with carcinoma in situ (Figs. 8 and 9). This suggests that dysplasia is a probable precursor of esophageal carcinoma (Fig. 10).

It was noteworthy that the area of dysplasia was extensive in some cases, especially of higher grade dysplasia (Figs. 11 and 12). This just accords with the fact that carcinoma in situ and early carcinoma of the esophagus show widely spread involvement (O’Gara and Horn 1955; Suckow et al. 1962; Ushigome et al. 1967; Akiyama et al. 1969). Circumstances were similar in dysplasia showing skip-wise lesions. Constitutional or generalized factors, other than local ones, should be considered in the exploration of the etiology of dysplasia.

The incidence of dysplasia of all grades in the grossly normal esophagus was nearly equal in 4 prefectures (Miyagi, Nara, Wakayama and Aomori). This means that among the above prefectures, irrespective of population risk of esophageal carcinoma, environmental factors inducing dysplasia of the esophageal epithelium exist universally. As to dysplasia of higher grade, the incidence was slightly higher in prefectures with high risk to esophageal carcinoma (Miyagi and Nara) except for Wakayama prefecture which had lower incidence, especially in female, despite of high risk to carcinoma (Table 2). Male preponderance of
esophageal carcinoma did not reflect in the incidence of dysplasia. The incidence of higher grade dysplasia seemed to be less frequent in the group of 50-69 years of age compared with that of over 70 years. However, the difference was statistically not significant. In order to solve these problems, epidemiological examination is required.

As to the location of higher grade dysplasia, involvement of distal 1/3 of the esophagus (57%) outnumbered the middle (37%). The above tendency in location of higher grade dysplasia did not accord with that of early carcinoma of the esophagus (Nabeya et al. 1974).

It was shown that the dysplasia intimately correlated in incidence with the existence of chronic esophagitis, ductal ectasia, hyperplasia of the duct epithelium and regeneration of the mucosal epithelium. Such relationships were particularly evident in Miyagi and Nara (Tables 3, 4 and 5). This suggests the possibility that dysplasia may develop under conditions of long-standing irritation upon the esophageal mucosa.

Although esophageal carcinoma is believed to be common in China, the incidence of dysplasia detected by exfoliative cytology (The Coordinating Groups for the Research of Esophageal Carcinoma, Honan Province and Chinese Academy of Medicine 1975) was far lower than that of ours. Some reasons may be sought in the difference, e.g. technical or racial.

Macroscopic findings of esophageal dysplasia are less characteristic, therefore it will be difficult to detect by endoscopic examinations. Endo and Nagayo (1974) did not mention about dysplasia or related lesions in their 925 cases of endoscopic investigation.

Any significant correlation between dysplasia and leukoplakia, most commonly detectable lesions in adult esophagus, was not obtained. This is in agreement with the claim that leukoplakia of the esophagus is not a premalignant lesion (Sandritter and Benke 1974).

Finally, it was suggested from our study that dysplasia of the esophageal epithelium might be regarded as a precancerous lesion. It is worth to re-stress that dysplasia, even restricted to higher grade lesion, is expected to be encountered at a rate of 12.09% in the distal 2/3 of the esophagus of older individuals in the age groups of high risk to esophageal carcinoma.

Acknowledgment

Materials from the Aomori, Nara and Wakayama prefectures were generously offered by Departments of Pathology at Hirosaki University, School of Medicine, Nara Medical College and Wakayama Medical College, respectively.

References


