Gastric xanthoma is a predictive marker for metachronous and synchronous gastric cancer

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AIM
To investigate predictive markers for metachronous and synchronous gastric cancer (GC), which can develop after endoscopic submucosal dissection (ESD).

METHODS
A total of 352 patients underwent ESD for early GC at NTT West Osaka Hospital between June 2006 and February 2016. Exclusion criteria were as follows: Remnant stomach, unknown Helicobacter pylori status, and endoscopic observation of the whole stomach outside our hospital. We analyzed data from 192 patients comprising 109 patients with solitary GC (Group A) and 83 with metachronous and synchronous GC (Group B). We retrospectively investigated the clinicopathological and endoscopic characteristics, and endoscopic risk score as predictive markers for GC.

RESULTS
The median age of Group B [72 years (interquartile range 63-78)] was significantly higher than that of Group A [66 years (interquartile range 61-74), respectively, \( P = 0.0009 \)]. The prevalence of intestinal metaplasia in Group B tended to be higher than that in Group A (57.8% vs 45.0%, \( P = 0.08 \)). The prevalence of gastric xanthoma (GX) in Group B was significantly higher than that in Group A (54.2% vs 32.1%, \( P = 0.003 \)). The atrophy score in Group B was significantly higher than that in Group A (\( P = 0.005 \)). Multivariate analysis revealed that higher age and the presence of GX were independently related to metachronous and synchronous GC (OR = 1.04).

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metachronous and synchronous GC, including GX and investigate predictive markers of the development of and synchronous GC also remains unknown. An accurate predictor of GC risk remains unclear. And the early GC (GX) has been reported as the predictive marker of GC risk was also announced. In 2015, the Kyoto global consensus (8­14) gastritis was elevated lesion by white light imaging, without image-enhanced endoscopy. This study was carried out with the approval of the NTT West Osaka Hospital Ethics Committee. Because of the anonymous nature of the date obtained after each patient had provided written informed consent for ESD, the requirement for informed consent was waived.

Statistical analysis
All statistical analyses were performed with EZR (Saitama Medical Center, Jichi Medical University, www.wjgnet.com).
Saitama, Japan), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria). More precisely, it is a modified version of R commander designed to add statistical functions frequently used in biostatistics[22]. Fisher’s exact test was performed to investigate the relationships between the two groups. Differences between the two groups were analyzed by Mann-Whitney U test when the data was not parametric. Multivariate logistic analysis was used to identify predictive markers of metachronous and synchronous GC. Age, sex, and baseline variates with P < 0.2 in univariate analysis were included in the multivariate logistic analysis. The threshold for significance was P < 0.05.

RESULTS

Clinicopathological characteristics of patients

The characteristics of the two patient groups are shown in Table 1.

The median ages in Group A and B were 66 [interquartile range (IQR) 61-74] and 72 [IQR 63-78] years, respectively (P = 0.0009). The proportion of male patients was high in both groups (84.4% vs 86.7%, P = 0.7). H. pylori status was positive for many patients in Group A and B (75.2% vs 68.7%, respectively, P = 0.4).

Regarding tumor location, lesion of the upper part of the stomach was least frequent. Median tumor size was 15 mm in both groups. The most frequent macroscopic type was 0-I. The scores for differentiated type were not significantly different between the two groups. Nodular gastritis was absent in all patients in this study.

Endoscopic characteristics

Endoscopic characteristics are shown in Table 2. Although the difference was not significant, the prevalence of severe atrophy and intestinal metaplasia in Group B tended to be higher than that in Group A (89.2% vs 79.8%, P = 0.1 and 57.8% vs 45.0%, P = 0.08). The prevalence of GX in Group B was significantly higher than that in Group A (54.2% vs 32.1%, P = 0.003). The number and size of GX were not significantly different between the two groups.

Endoscopic score for GC risk

The endoscopic score for GC risk is reported in Table 3. The atrophy score in Group B was significantly higher than that in Group A (P = 0.005). The scores for intestinal metaplasia, fold swelling, and diffuse redness, and the total score were not significantly different between the two groups. Nodular gastritis was absent in all patients in this study.

Multivariate logistic analysis

Age, male sex, severe atrophy, presence of intestinal metaplasia, and presence of GX were subjected to multivariate logistic analysis. As shown in Table 4, higher age and the presence of GX were independently related to metachronous and synchronous GC.

DISCUSSION

In the present study, we compared the characteristics of 109 patients with solitary GC to those of 83 patients with metachronous and synchronous GC in order to identify predictive markers for metachronous and synchronous GC. Multivariate logistic analysis revealed that high age and the presence of GX were independently related to metachronous and synchronous GC.

The results of recent studies indicated that male sex, multiple initial GC, severe atrophy, and multiple GC before successful H. pylori eradication were independent risk factors for metachronous GC[13,14]. After performing...
univariate analysis, we carried out multivariate logistic analysis using male sex and severe atrophy as variates, but our results revealed that these two markers were not predictive of metachronous and synchronous GC. This finding may reflect the fact that most patients in this study were male and showed severe atrophy in both groups.

Endoscopic findings related to the development of GC have been previously reported. Of these, five endoscopic findings were confirmed; atrophy, intestinal metaplasia, fold swelling, nodular gastritis, and diffuse redness. A subsequent study reported the endoscopic score for GC risk; however, the usefulness of this score remains unclear. After performing univariate analysis, we carried out multivariate logistic analysis using severe atrophy and intestinal metaplasia as variates. However, our results indicated that these two markers were not predictive of metachronous and synchronous GC. Further investigations are necessary to evaluate the usefulness of the endoscopic score for GC risk.

GX, a localized non-neoplastic accumulation of foamy histiocytes in the lamina propria of the inflamed gastric mucosa, is occasionally found during EGD. GX is a positive indicator of H. pylori and persists after eradication therapy. GX has received little attention clinically, perhaps because it is considered a benign entity. A retrospective cohort study reported that the presence of GX was significantly associated with the presence of GC. Another cohort study performed at the same hospital reported that GX was a useful marker for predicting the development of GC by performing endoscopic follow-up examinations. However, both these studies did not investigate GX as a predictive marker for metachronous and synchronous GC. In our study, univariate analysis revealed that GX was significantly more prevalent in Group B than in Group A. In addition, results of multivariate logistic analysis indicated that GX was a predictive marker for metachronous and synchronous GC. To our knowledge, this is first report of the presence of GX as a useful predictive marker for metachronous and synchronous GC.

Why does GC develop more frequently in patients with GX? Increased release of oxygen free radicals may be involved in the formation of GX. On the other hand, the presence of GX may reflect the severity and long duration of chronic gastritis, which is a risk factor for GC development. Because of the same reason, GX may be more frequent in Group B than Group A. However, further studies are required to elucidate this link.

Our study has some limitations. First, it was a retrospective single-center study. Second, the sample size was small. Finally, we did not analyze inter-observer variability in the assessment of endoscopic images.

In summary, our results revealed that higher age and the presence of GX were independently related to metachronous and synchronous GC. These findings, especially the predictive value of the presence of GX, could improve the timely detection and treatment of metachronous and synchronous GC. Further investigations are necessary to confirm the predictive value of these markers.

### COMMENTS

**Background**

Predictive markers for the development of metachronous and synchronous gastric cancer (GC) have not been extensively studied. In addition, it is often difficult to clearly distinguish metachronous GC from synchronous GC because of missed detection of synchronous GC. And the usefulness of endoscopic score for GC risk and gastric xanthoma (GX) as the predictive markers of metachronous and synchronous GC remains unknown.

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**Table 2** Endoscopic characteristics of the two groups (%)  

|                  | Group A (n = 109) | Group B (n = 83) | P value |
|------------------|-------------------|------------------|---------|
| Severe atrophy   | 87 (79.8)         | 74 (89.2)        | 0.1     |
| Intestinal       | 49 (45.0)         | 48 (57.8)        | 0.08    |
| metaplasia       |                   |                  |         |
| Gastric xanthoma | 35 (32.1)         | 45 (54.2)        | 0.003   |

**Table 3** Endoscopic score of risk for gastric cancer of the two groups  

|                  | Group A (n = 109) | Group B (n = 83) | P value |
|------------------|-------------------|------------------|---------|
| Atrophy          | 0                 | 0                | 0.005   |
| 1                | 1                 | 1                |         |
| 2                | 99                | 83               |         |
| Intestinal       | 0                 | 0                | 0.1     |
| metaplasia       | 60                | 35               |         |
| 1                | 33                | 34               |         |
| 2                | 14                | 14               |         |
| Fold swelling    | 0                 | 0                | 0.6     |
| 1                | 99                | 73               |         |
| 1                | 10                | 10               |         |
| Nodular gastritis| 0                 | 109              | 1.0     |
| 1                | 1                 | 0                |         |
| Diffuse redness  | 0                 | 4                | 0.5     |
| 1                | 23                | 25               |         |
| 2                | 82                | 58               |         |
| Total score, median [IQR] | 4 [4-5] | 4 [4-5] | 0.1 |

IQR: Interquartile range.

**Table 4** Multivariate analysis of predictive marker of metachronous and synchronous gastric cancer  

|                  | Odds ratio | P value |
|------------------|------------|---------|
| Age              | 1.04 (1.01-1.08) | 0.02   |
| Male             | 1.38 (0.57-3.34) | 0.47   |
| Severe atrophy   | 1.68 (0.70-4.05) | 0.25   |
| Intestinal       | 1.35 (0.71-2.54) | 0.36   |
| metaplasia       |            |         |
| Gastric xanthoma | 2.11 (1.14-3.99) | 0.02   |
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