Abstract

EBV involvement in gastric cancer is characterized by episomal monoclonality, high antibody titers, EBV encoded small RNA and EBV nuclear antigen 1 expression in all tumor cells, and in the intramucosal stage, by a unique morphology. EBV involvement varies by population (~7% of gastric cancers in Japan and >15% in Western countries), sex, histological type, and tumor location. The present study compares frequency of lymph node metastasis (LNM) between 170 EBV-positive and 1590 EBV-negative gastric cancer cases in Japan by level of invasiveness. Frequency of LNM increased with increasing depth of invasiveness but was consistently and significantly greater for EBV-negative cases (P = 0.0018). In particular, there were no instances of LNM among EBV-negative gastric cancer cases in Japan by level of invasiveness. Frequency of LNM increased with increasing depth of invasiveness but was consistently and significantly greater for EBV-negative cases (P = 0.0018). In particular, there were no instances of LNM among EBV-negative gastric cancer cases in Japan by level of invasiveness. Frequency of LNM increased with increasing depth of invasiveness but was consistently and significantly greater for EBV-negative cases (P = 0.0018). In particular, there were no instances of LNM among EBV-negative gastric cancer cases in Japan by level of invasiveness.

Introduction

EBV involvement, as determined by EBER in situ hybridization, occurs in ~7% of gastric cancers in Japan and >15% in Western countries. Characteristics of EBV-associated gastric cancers include episomal monoclonality, high antibody titers, and EBER and EBV nuclear antigen 1 expression in all tumor cells. EBV involvement is negatively associated with lymph node metastasis. Also, the possibility that EBV-positive, noninvasive gastric cancers may not require lymph node dissection suggests that routine assay of biopsy specimens for EBV involvement could be important in populations, like that of Japan, where early gastric cancers are seen frequently.

Results

As expected, LNM increased with increasing tumor depth (P < 0.0001 for nonhomogeneity; all Ps are adjusted for other factors) and varied by histology (P = 0.0004). Metastasis was strongly, and negatively, associated with EBV involvement (P = 0.0018); 53 of 170 EBV-positive cases (31%) had LNM as compared with 764 of 1590 EBV-negative cases (48%). This negative association was observed at all four levels of tumor depth, among which metastasis rates varied widely (Table 1).

Discussion

Our findings suggest that testing biopsy specimens for EBV involvement before surgery would provide valuable information about the appropriateness of conservative therapies such as...
Table I  LNM by EBV involvement and depth of invasion

<table>
<thead>
<tr>
<th>Depth</th>
<th>EBV-negative</th>
<th></th>
<th>EBV-positive</th>
<th></th>
<th>Total</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Frequency</td>
<td>(%)</td>
<td>Frequency</td>
<td>(%)</td>
<td>Frequency</td>
<td>(%)</td>
</tr>
<tr>
<td>Mucosa</td>
<td>5/284</td>
<td>(1.8)</td>
<td>0/30</td>
<td>(0)</td>
<td>5/314</td>
<td>(1.6)</td>
</tr>
<tr>
<td>Submucosa</td>
<td>48/278</td>
<td>(17.3)</td>
<td>0/45</td>
<td>(0)</td>
<td>48/323</td>
<td>(14.9)</td>
</tr>
<tr>
<td>Muscular layer</td>
<td>69/185</td>
<td>(37.3)</td>
<td>5/17</td>
<td>(29.4)</td>
<td>74/202</td>
<td>(36.6)</td>
</tr>
<tr>
<td>Serosa</td>
<td>642/843</td>
<td>(76.2)</td>
<td>48/78</td>
<td>(61.5)</td>
<td>690/921</td>
<td>(74.9)</td>
</tr>
<tr>
<td>Total</td>
<td>764/1590</td>
<td>(48.1)</td>
<td>53/170</td>
<td>(31.2)</td>
<td>817/1760</td>
<td>(46.4)</td>
</tr>
</tbody>
</table>

endoscopic strip resection, laparoscopic resection, and local resection without lymph node dissection in cases of intramucosal cancer and invasive cancer restricted to the submucosa, even when the lesion is ulcerated. Further investigation of this possibility by clinical trial may be appropriate. Early gastric cancers, with limited invasion, are seen fairly frequently in Japan, where gastric cancer rates are very high and large-scale screening programs are in place. We found no instances of LNM among 75 EBV-positive cases with early cancers as compared with 53 among 562 EBV-negative cases (odds ratio, 0; 95% confidence limits, 0–0.20; adjusted for tumor depth and histology).

For more deeply invasive cancers, the frequency of LNM was fairly high, even among EBV-positive cases (29 and 62% for muscular layer and serosa, respectively), which suggests that a decision on lymph node resection probably would not depend upon whether the cancer was positive or negative for EBV. A statistically significant difference was apparent, nevertheless (odds ratio, 0.54; 95% confidence limits, 0.34–0.88).

Overall, our results suggest that genetic control of metastasis may differ between EBV-positive and EBV-negative gastric cancers. That possibility warrants further study using more probing investigative techniques.

References

Epstein-Barr virus involvement in gastric cancer: biomarker for lymph node metastasis.

M Tokunaga and C E Land


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