Author's response to reviews

Title: Early duodenal adenocarcinoma resembling submucosal tumor cured with endoscopic resection: a case report

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Author's response to reviews: see over
Dear Professor Kidd,

We are resubmitting our revised manuscript titled “Early duodenal adenocarcinoma resembling submucosal tumor cured with endoscopic resection: a case report” (Manuscript ID 9493236006751721) for publication as a Case report in “Journal of Medical Case Reports”.

We appreciate the thoughtful comments of the reviewers. As suggested by the reviewers, we are resubmitting this article after it has been fully revised according to their comments.

A point-by-point reply to their comments appears following this cover letter. We appreciate your re-consideration of this work for publication.

Yours sincerely,

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I would like to thank you for your comments on our article. Your thoughtful comments are very insightful and we would like to follow your advice about the manuscript.

**Reviewer: Dr. Rudolf Mennigen**

Major comments:

1) Did the patient have any symptoms?

2) Please provide details concerning the medical history of the patient.

   According to this comment, we have added a sentence as follows:

   **Case presentation, paragraph 1**

   A 65-year-old Japanese man, with no symptoms and only receiving oral medication for hypertension, underwent an esophagastroduodenoscopy (EGD) for a medical checkup in November 2009.

3) How do you explain the delay of six months between diagnosis and surgical therapy?

   According to this comment, we have changed the text as follows:

   **Case presentation, paragraph 1**

   A polypoid lesion, about 10 mm in diameter with a deep depression on top, was found on the opposite side of the Vater papilla in the second portion of the duodenum (Fig. 1A). The lesion was covered by normal mucosa except in the depressed portion which showed tense surface mucosa. The lesion was similar in appearance to a SMT with a central depression. Multiple biopsies were taken from the lesion, but all of the specimens showed normal duodenal mucosa. The lesion was strongly suspected to be a malignant tumor and six more biopsies were taken from the lesion during a second EGD three months later. Only one of the six biopsy specimens revealed adenocarcinoma.
4) Figures 1a and 1b basically show the same image, one of the figures should be deleted.

Multiple biopsies can make a depression at the biopsied area. We would like to show the tumor originally had a depressed area before the biopsies in Figure 1a. Therefore, we have added the dates of EGD in the legends of Figure 1a and 1b as follows:

Figure legends

Fig. 1. Endoscopic findings.

(A) Conventional endoscopy before multiple biopsies at a medical checkup in November 2009 showed a submucosal tumor-like polypoid lesion with a central deep depression.

(B) In work-up prior to surgery in May 2010, conventional endoscopy showed a submucosal tumor-like polypoid lesion with depression. The lesion was decreased in height and had tense surface mucosa compared with the lesion seen during the initial esophagogastrroduodenoscopy at the medical checkup in November 2009.

5) Please comment on the applied technique of endoscopically resection (snare? submucosal dissection?)

According to this comment, we have added the following sentence:

Case presentation, paragraph 2

We predicted that it was possible to remove the tumor by ER and the tumor was removed using a conventional endoscopic mucosal resection (EMR) technique with submucosal injection of glycerin solution and the snare method, instead of by pancreaticoduodenectomy as planned.

6) Please comment on the exact location of the tumor, especially the distance to
the papilla of Vater.

In line with this comment, we have changed the text as follows:

Case presentation, paragraph 1

A polypoid lesion, about 10 mm in diameter with a deep depression on top, was found on the opposite side of the Vater papilla in the second portion of the duodenum (Fig. 1A).

7) Discussion: You "reviewed several reports and investigated the clinicopathological features of 27 lesions in 27 patients." The cited literature (3-5), however, includes three case reports. So which literature is the basis of your review of the literature? Perhaps a brief table with key facts of reported cases so far would be helpful.

A previous report reviewed 24 cases of colorectal adenocarcinoma resembling submucosal tumors [Ref #2]. Additionally, we reviewed 3 cases found in other previous reports [Refs #3-5], thus totaling 27 lesions in 27 patients.

Accordingly we have made a brief table as follows:
Table 1. Published cases of carcinoma resembling submucosal tumor in the duodenum and colon

<table>
<thead>
<tr>
<th>Case (Ref.)</th>
<th>Age (y)</th>
<th>Gender</th>
<th>Location of lesion</th>
<th>Size of lesion (mm)</th>
<th>Central depression</th>
<th>Depth of cancerous invasion</th>
<th>Inverted growth</th>
<th>Histologic Diagnosis</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (2)</td>
<td>71</td>
<td>M</td>
<td>S</td>
<td>20</td>
<td>present</td>
<td>adv</td>
<td>absent</td>
<td>well</td>
<td>SR</td>
</tr>
<tr>
<td>2 (2)</td>
<td>42</td>
<td>F</td>
<td>R</td>
<td>50</td>
<td>present</td>
<td>adv</td>
<td>absent</td>
<td>well</td>
<td>SR</td>
</tr>
<tr>
<td>3 (2)</td>
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<td>F</td>
<td>A</td>
<td>80</td>
<td>present</td>
<td>adv</td>
<td>absent</td>
<td>poor</td>
<td>SR</td>
</tr>
<tr>
<td>4 (2)</td>
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<td>M</td>
<td>A</td>
<td>50</td>
<td>present</td>
<td>adv</td>
<td>absent</td>
<td>mod</td>
<td>SR</td>
</tr>
<tr>
<td>5 (2)</td>
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<td>present</td>
<td>sm</td>
<td>absent</td>
<td>well</td>
<td>SR</td>
</tr>
<tr>
<td>6 (2)</td>
<td>44</td>
<td>M</td>
<td>R</td>
<td>80</td>
<td>present</td>
<td>adv</td>
<td>absent</td>
<td>well</td>
<td>SR</td>
</tr>
<tr>
<td>7 (2)</td>
<td>44</td>
<td>M</td>
<td>D</td>
<td>50</td>
<td>present</td>
<td>adv</td>
<td>absent</td>
<td>muc</td>
<td>SR</td>
</tr>
<tr>
<td>8 (2)</td>
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<td>M</td>
<td>A</td>
<td>N.D</td>
<td>present</td>
<td>adv</td>
<td>absent</td>
<td>mod</td>
<td>SR</td>
</tr>
<tr>
<td>9 (2)</td>
<td>64</td>
<td>M</td>
<td>R</td>
<td>10</td>
<td>absent</td>
<td>sm</td>
<td>absent</td>
<td>mod</td>
<td>SR</td>
</tr>
<tr>
<td>10 (2)</td>
<td>76</td>
<td>F</td>
<td>R</td>
<td>35</td>
<td>present</td>
<td>adv</td>
<td>absent</td>
<td>muc</td>
<td>SR</td>
</tr>
<tr>
<td>11 (2)</td>
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<td>M</td>
<td>D</td>
<td>15</td>
<td>present</td>
<td>sm</td>
<td>absent</td>
<td>mod</td>
<td>SR after ER</td>
</tr>
<tr>
<td>12 (2)</td>
<td>57</td>
<td>M</td>
<td>S</td>
<td>28</td>
<td>present</td>
<td>adv</td>
<td>absent</td>
<td>well</td>
<td>SR</td>
</tr>
<tr>
<td>13 (2)</td>
<td>62</td>
<td>M</td>
<td>S</td>
<td>10</td>
<td>present</td>
<td>adv</td>
<td>absent</td>
<td>poor</td>
<td>SR after ER</td>
</tr>
<tr>
<td>14 (2)</td>
<td>48</td>
<td>M</td>
<td>T</td>
<td>45</td>
<td>present</td>
<td>adv</td>
<td>absent</td>
<td>poor</td>
<td>SR</td>
</tr>
<tr>
<td>15 (2)</td>
<td>53</td>
<td>M</td>
<td>R</td>
<td>14</td>
<td>present</td>
<td>sm</td>
<td>absent</td>
<td>well</td>
<td>SR</td>
</tr>
<tr>
<td>16 (2)</td>
<td>48</td>
<td>M</td>
<td>A</td>
<td>15</td>
<td>present</td>
<td>adv</td>
<td>absent</td>
<td>mod</td>
<td>SR</td>
</tr>
<tr>
<td>17 (2)</td>
<td>52</td>
<td>M</td>
<td>S</td>
<td>10</td>
<td>present</td>
<td>adv</td>
<td>absent</td>
<td>mod</td>
<td>SR</td>
</tr>
<tr>
<td>18 (2)</td>
<td>80</td>
<td>M</td>
<td>A</td>
<td>80</td>
<td>absent</td>
<td>adv</td>
<td>absent</td>
<td>poor</td>
<td>SR</td>
</tr>
<tr>
<td>19 (2)</td>
<td>67</td>
<td>M</td>
<td>A</td>
<td>4</td>
<td>present</td>
<td>sm</td>
<td>absent</td>
<td>well</td>
<td>SR after ER</td>
</tr>
<tr>
<td>20 (2)</td>
<td>70</td>
<td>M</td>
<td>A</td>
<td>15</td>
<td>present</td>
<td>sm</td>
<td>absent</td>
<td>mod</td>
<td>SR</td>
</tr>
<tr>
<td>21 (2)</td>
<td>58</td>
<td>M</td>
<td>S</td>
<td>12</td>
<td>present</td>
<td>adv</td>
<td>absent</td>
<td>well</td>
<td>SR</td>
</tr>
<tr>
<td>22 (2)</td>
<td>69</td>
<td>F</td>
<td>C</td>
<td>18</td>
<td>present</td>
<td>sm</td>
<td>absent</td>
<td>mod</td>
<td>SR</td>
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<tr>
<td>23 (2)</td>
<td>70</td>
<td>M</td>
<td>S</td>
<td>14</td>
<td>present</td>
<td>sm</td>
<td>absent</td>
<td>mod</td>
<td>SR</td>
</tr>
<tr>
<td>24 (2)</td>
<td>54</td>
<td>M</td>
<td>S</td>
<td>12</td>
<td>present</td>
<td>sm</td>
<td>absent</td>
<td>mod</td>
<td>SR</td>
</tr>
<tr>
<td>25 (3)</td>
<td>51</td>
<td>M</td>
<td>S</td>
<td>10</td>
<td>present</td>
<td>sm</td>
<td>present</td>
<td>well</td>
<td>ER</td>
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<tr>
<td>26 (4)</td>
<td>60</td>
<td>M</td>
<td>A</td>
<td>15</td>
<td>present</td>
<td>sm</td>
<td>present</td>
<td>well</td>
<td>SR after ER</td>
</tr>
<tr>
<td>27 (5)</td>
<td>62</td>
<td>M</td>
<td>A</td>
<td>40</td>
<td>present</td>
<td>adv</td>
<td>absent</td>
<td>muc</td>
<td>SR</td>
</tr>
<tr>
<td>28 (our case)</td>
<td>65</td>
<td>M</td>
<td>Duodenum</td>
<td>10</td>
<td>present</td>
<td>m</td>
<td>present</td>
<td>well</td>
<td>ER</td>
</tr>
</tbody>
</table>

A, ascending colon; adv, advanced cancer invading deeper than the muscularis propria; C, cecum; D, descending colon; ER, endoscopic resection; F, female; M, male; m, mucosae; mod, moderately-differentiated adenocarcinoma; muc, mucinous carcinoma; N.D, not described; poor, poorly-differentiated adenocarcinoma; R, rectum; S, sigmoid colon; sm, submucosa; SR, surgical resection; T, transverse colon; well, well-differentiated adenocarcinoma.
8) Please add the following topics to your discussion:

Role of endoscopic ultrasound in planning endoscopic resection, accuracy of endoscopic ultrasound;

We have added the following sentences according to your comment:

Discussion, paragraph 5

Mucosal cancers are good candidates for endoscopic resection because there is no risk of lymph node metastasis [11]. Therefore, it is important to estimate the depth of invasion of duodenal carcinoma and to differentiate mucosal cancer from cancer invading to the submucosal layer or deeper. There are no reports evaluating the depth of invasion in duodenal adenocarcinoma by EUS. However, in colorectal cancers, several studies have evaluated the usefulness of EUS for diagnosing the invasion depth [11-13]. The overall diagnostic accuracy rates of EUS were 75% - 80% [12,13]. One problem with the diagnosis of tumor depth by EUS was overstaging while no understaging was recorded [13]. Thus, if EUS of the present case demonstrates tumor invasion has not reached the muscularis propria, but is up to the submucosal layer, it has a great chance of removal by ER. Therefore we made the decision to remove the tumor by ER in this case mainly based on the EUS findings.

Additional References


endoscopic resection as "total biopsy", if resection incomplete, duodenopancreatectomy can still be performed;

In light of your suggestion, we have added the following:

**Discussion, paragraph 6**

In this case, we performed ER as a total biopsy. If histology from the ER had revealed the tumor was confined to the mucosal layer and the horizontal margin was positive, we would have planned an additional ER or endoscopic coagulation therapy. Otherwise, if histology had shown that the tumor had submucosal invasion or lymphovascular invasion, or was positive for the vertical margin, we would have planned a partial resection or pancreaticoduodenectomy with lymphadenectomy

relation of the tumor to the papilla of Vater (endoscopic resection feasible?):

Another reviewer also indicated this point. We have changed the text as follows:

**Case presentation, paragraph 1**

A polypoid lesion, about 10 mm in diameter with a deep depression on top, was found on the opposite side of the Vater papilla in the second portion of the duodenum (Fig. 1A).
prognosis of duodenal cancer.

According to this comment, we have added sentences as follows:

Discussion, paragraph 1

The prognosis for duodenal adenocarcinoma is reported to be a 5-year survival rate of less than 30% [7]. Thus, the prognosis is very poor in patients with an advanced stage [8]. If the duodenal adenocarcinoma is found in its early stage, then endoscopic curative resection is possible [6]. So, it is very important to detect duodenal adenocarcinoma in the early stage to result in a good prognosis.

Additional References


9) Please provide exact pTNM status after resection.

According to this comment, we have changed the text as follows:

Case presentation, paragraph 3

Histology results from the ER confirmed the tumor was a well-differentiated adenocarcinoma confined to the muscularis mucosae with no lymphovascular invasion and negative margins (Tis N0 M0, Stage 0); complete resection was achieved.
Reviewer: Dr. Hironori Tsujimoto

Major comments:

1. The author should describe the procedure of ER more in detail, i.e., EMR-c or ESD? The other reviewer also made the same comment. Please refer to point No.5 on page 3 of this response letter.

2. The author should state the postoperative course after ER. was it uneventful or eventful?

   According to this comment, we have added the following sentences:

   Case presentation, paragraph 2

   The EMR was performed with no complications and the patient had a straightforward post-ER course. The patient was discharged from the hospital a week after ER.

3. EUS showed M cancer in the duodenum. Why the authors want to perform PD at first? Is the SMT-like cancer easy to have LN metastasis even if M cancer? The author should describe this issue.

   When the SMT-like lesion was found, a doctor in private practice considered the tumor to be a duodenal carcinoma invading the submucosal layer or deeper. He estimated the SMT-like lesion would have a substantial risk of LN metastasis. So, he referred the patient to a surgeon in our hospital.

   EUS demonstrated that the SMT-like tumor was not invading the deep submucosa or muscularis propria. CT showed neither lymph node swelling nor metastatic tumor. Therefore, the SMT-like tumor behaved as a potentially resectable carcinoma by ER.
- Please replace the header “Background” with “Introduction”.

We have replaced the heading “Background” with “Introduction”.

- Please include the ethnicity of the patient in the abstract and case presentation sections.

We have added the ethnicity of the patient in the Abstract and Case Presentation as follows:

Abstract, Case presentation

A 65-year-old Japanese man was diagnosed with a SMT-like adenocarcinoma in the duodenum.

Case presentation, paragraph 1

A 65-year-old Japanese man, with no symptoms and only receiving oral medication for hypertension, underwent an esophagogastroduodenoscopy (EGD) for a medical checkup in November 2009.

- Please replace date found in the case presentation to the amount of time this occurred before the presentation of the case report.

According to this comment, we have changed the text as follows:

Discussion, paragraph 4

A previous report in 2005 reviewed 24 cases of colorectal adenocarcinoma resembling SMT [2]. We found three more cases in previous reports which were published in 2004 to 2007 [3-5],...

- Please include the following as the last sentence of the Consent section: A copy of the
written consent is available for review by the Editor-in-Chief of this journal.

We have added this sentence to the Consent section.