Duodenal gangliocytic paraganglioma: report of two cases and review of literature

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Abstract: We report two cases of Gangliocytic paraganglioma (GP), one of which was accompanied by lymph node metastasis. Histologically, the tumor was composed of three morphologically distinct cell populations: spindle cells, ganglion-like cells and epithelioid cells. The epithelioid cells were positive for cytokeratin (AE1/AE3), synaptophysin (Syn), chromogranin A (CgA), CD56 and progesterone receptor (PR). Ganglion-like cell types showed positive reactivity for Syn and CD56. In contrast, the spindle-shaped cells showed positive reactivity for S-100. The patient with lymph node metastasis has a good prognosis. Nonetheless, close surveillance is still necessary for patients with GP because a few cases of GP with regional lymph node metastasis and even distant metastasis have been published, including a malignant case of GP showing a lethal course.

Keywords: Gangliocytic paraganglioma, synaptophysin, chromogranin A, CD117

Introduction

Gangliocytic paraganglioma (GP) is a rare tumor that is mainly located in the second portion of the duodenum [1, 2]. It accounts for 6% to 9% of duodenal gastrointestinal neuroendocrine tumors (NETs), ranking the third most frequent histopathologic type after gastrinomas and somatostatinomas [3]. It is featured by its triphasic cellular differentiation, composed of epithelioid neuroendocrine cells, spindle-shaped cells with Schwannian cell differentiation and ganglion-like cells [1]. According to the World Health Organization (WHO) classification, this tumor has generally been regarded as benign, but a few cases with regional lymph node metastasis and even distant metastasis have been reported. To date, 23 cases of GP with lymph node metastasis and 3 cases with distant metastasis have been published (Table 1). Herein we presented two cases of GP, one of which was accompanied by lymph node metastasis (case 1).

Case report

Case 1

A 42-year-old man presented with melana and dizziness for 3 weeks. He was admitted to a local hospital. He denied abdominal pain, nausea, vomiting and fever. His laboratory data revealed anemia (blood hemoglobin value 56 g/L). Computed tomographic (CT) scans showed a mass in the third portion of the duodenum. It was suspected as a leiomyoma. For further examination and treatment he was then transferred to our hospital. CT scans also revealed a mass with 31 mm×24 mm in the third portion of the duodenum. Endoscopic ultrasonography showed a polypoid tumor in duodenum and ulceration on the surface of the lesion. The patient underwent local surgical excision on 7/22/2010. Unfortunately, the follow-up of the patient is not established.

Case 2

A 49-year-old man was admitted to our institute with upper abdominal pain for nine days. He denied nausea, vomiting and changes in bowel habits. Laboratory results were within normal range. CT scans revealed a mass with 38 mm×25 mm near the head of pancreas (Figure 1), involving the second portion of the duodenum. Enlarged peripancreatic lymph nodes were observed. Endoscopic ultrasonography detected a lesion with 33 mm×18 mm near the head of pancreas, involving the second portion of the duodenum. The surface of the tumor was
Table 1. Clinical pathological findings of gangliocytic paraganglioma with lymph node or distant metastasis

<table>
<thead>
<tr>
<th>No.</th>
<th>Reference</th>
<th>Age (yr)/gender</th>
<th>Tumor site</th>
<th>Tumor size (mm)</th>
<th>Lymph node metastasis</th>
<th>Distant metastasis</th>
<th>Treatment</th>
<th>Follow up (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Buchler et al [4]</td>
<td>50/male</td>
<td>Ampulla of Vater</td>
<td>30</td>
<td>Yes</td>
<td>No</td>
<td>LR</td>
<td>NED 20 mo</td>
</tr>
<tr>
<td>2</td>
<td>Korbi et al [5]</td>
<td>73/female</td>
<td>Duodenum</td>
<td>NA</td>
<td>Yes</td>
<td>No</td>
<td>WP</td>
<td>NA</td>
</tr>
<tr>
<td>3</td>
<td>Inai et al [6]</td>
<td>17/male</td>
<td>Duodenum</td>
<td>20</td>
<td>Yes</td>
<td>No</td>
<td>WP</td>
<td>NED 32 mo</td>
</tr>
<tr>
<td>4</td>
<td>Hashimoto et al [7]</td>
<td>47/male</td>
<td>Second portion of the duodenum</td>
<td>65</td>
<td>Yes</td>
<td>No</td>
<td>WP</td>
<td>NED 14 mo</td>
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<tr>
<td>5</td>
<td>Dookhan et al [8]</td>
<td>41/male</td>
<td>Duodenum</td>
<td>25</td>
<td>Yes</td>
<td>No</td>
<td>LR+WP</td>
<td>Recurrence 11 years after first LR</td>
</tr>
<tr>
<td>6</td>
<td>Takabayashi et al [9]</td>
<td>63/female</td>
<td>Papilla of Vater</td>
<td>32</td>
<td>Yes</td>
<td>No</td>
<td>WP</td>
<td>NED 24 mo</td>
</tr>
<tr>
<td>7</td>
<td>Tomic et al [10]</td>
<td>74/female</td>
<td>Pancreas</td>
<td>40</td>
<td>Yes</td>
<td>No</td>
<td>WP</td>
<td>NED 19 mo</td>
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<tr>
<td>9</td>
<td>Sundararajan et al [12]</td>
<td>67/female</td>
<td>Second portion of the duodenum</td>
<td>50</td>
<td>Yes</td>
<td>No</td>
<td>WP</td>
<td>NED 9 mo</td>
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<tr>
<td>10</td>
<td>Bucher et al [13]</td>
<td>31/female</td>
<td>Papilla of Vater</td>
<td>30</td>
<td>Yes</td>
<td>No</td>
<td>WP</td>
<td>NED 44 mo</td>
</tr>
<tr>
<td>11</td>
<td>Wong et al [14]</td>
<td>49/female</td>
<td>Duodenum</td>
<td>14</td>
<td>Yes</td>
<td>No</td>
<td>WP+RT</td>
<td>NED 12 mo</td>
</tr>
<tr>
<td>12</td>
<td>Witkiewicz et al [15]</td>
<td>38/female</td>
<td>Papilla of Vater</td>
<td>15</td>
<td>Yes</td>
<td>No</td>
<td>LR+WP</td>
<td>NA</td>
</tr>
<tr>
<td>13</td>
<td>Mann et al [16]</td>
<td>17/female</td>
<td>Duodenum</td>
<td>NA</td>
<td>Yes</td>
<td>No</td>
<td>WP</td>
<td>NED 12 mo</td>
</tr>
<tr>
<td>14</td>
<td>Okubo et al [1]</td>
<td>61/male</td>
<td>Papilla of Vater</td>
<td>30</td>
<td>Yes</td>
<td>No</td>
<td>WP</td>
<td>NED 6 mo</td>
</tr>
<tr>
<td>15</td>
<td>Saito et al [17]</td>
<td>28/male</td>
<td>Papilla of Vater</td>
<td>NA</td>
<td>Yes</td>
<td>No</td>
<td>WP</td>
<td>NA</td>
</tr>
<tr>
<td>16</td>
<td>Sandmann et al [18]</td>
<td>62/female</td>
<td>Ampulla of Vater</td>
<td>50</td>
<td>Yes</td>
<td>No</td>
<td>LR</td>
<td>NA</td>
</tr>
<tr>
<td>17</td>
<td>Uchida et al [19]</td>
<td>67/female</td>
<td>Second portion of the duodenum</td>
<td>NA</td>
<td>Yes</td>
<td>No</td>
<td>WP</td>
<td>NA</td>
</tr>
<tr>
<td>18</td>
<td>Rowsell et al [20]</td>
<td>52/female</td>
<td>Duodenum</td>
<td>10</td>
<td>Yes</td>
<td>Liver</td>
<td>LR</td>
<td>NED 27 mo</td>
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<tr>
<td>19</td>
<td>Ogata et al [21]</td>
<td>16/male</td>
<td>Ampulla of Vater</td>
<td>25</td>
<td>Yes</td>
<td>No</td>
<td>WP</td>
<td>NED 36 mo</td>
</tr>
<tr>
<td>20</td>
<td>Barret et al [22]</td>
<td>51/female</td>
<td>Duodenal papilla</td>
<td>35</td>
<td>Yes</td>
<td>No</td>
<td>WP</td>
<td>NED 8 yr</td>
</tr>
<tr>
<td>21</td>
<td>Bin Li et al [23]</td>
<td>47/male</td>
<td>Duodenal papilla</td>
<td>30</td>
<td>Yes</td>
<td>Liver and pelvic cavity</td>
<td>WP+RT+CT+pelvic mass resection</td>
<td>Die 13 mo after initial surgery</td>
</tr>
<tr>
<td>22</td>
<td>Huijuan Shi et al [24]</td>
<td>47/male</td>
<td>Ampulla of Vater</td>
<td>40</td>
<td>Yes</td>
<td>No</td>
<td>WP</td>
<td>NED 24 mo</td>
</tr>
<tr>
<td>23</td>
<td>Okubo et al [25]</td>
<td>74/female</td>
<td>Second portion of the duodenum</td>
<td>23</td>
<td>Yes</td>
<td>No</td>
<td>WP</td>
<td>NED 6 mo</td>
</tr>
</tbody>
</table>

LR: Local resection; WP: Whipple procedure; CT: chemotherapy; RT: Radiotherapy; NA: Not available; NED: No evidence of disease.
smooth without bleeding or ulceration. The patient underwent pancreaticoduodenectomy and lymph node dissection on 2/13/2012.

Subsequently, the patient received chemotherapy for 5 cycles.

To date, the patient remains well and no recurrence has been recognized in a three-year follow-up period.

**Pathological findings**

Grossly, a mass measuring 30mm in the largest dimension was found in the resected specimen of case 1. It was covered by the mucosa. Ulceration was found on the surface. The surgical specimen of case 2 consisted of the duodenum, bile duct, gallbladder and head of the pancreas. A solid tumor 40×30×30 mm in size was located between the head of pancreas and the duodenum papilla. The mucosa was smooth without bleeding or ulceration. A total of nine lymph nodes were also removed.
Two cases report and literature review

Microscopically, the tumor in case 1 was localized in submucosal layer, showing an expansive growth pattern (Figure 2). The lesion focally invaded the peri-tissue. Ulceration was observed on the surface of the mucosa. The tumor in case 2 involved the whole wall of the duodenum (Figure 3), encroaching on the pancreas (Figure 4). The microscopical characteristics of the two cases were similar. The tumor was composed of three morphologically distinct cell populations: spindle cells, ganglion-like cells and epithelioid cells. The epithelial cells arranged in the nests and trabeculae, with round to oval-shaped nucleus and pale eosinophilic cytoplasm. The spindle cells, with an elongated nucleus and attenuated eosinophilic cytoplasm, formed slender fascicles encompassing the nests of epithelioid cells (Figure 5). Ganglion-like cells were rarely seen and had a round nucleus with conspicuous nucleolus (Figure 6). There was no mitotic figure or necrosis in the foci. Moreover, in case 2, the tumor cells focally mixed with the proliferative bile ducts (Figure 7).

The metastatic tumor was found in three of nine lymph nodes in case 2. The histological features in the metastases were identical with the primary lesion (Figure 8).

**Immunohistochemical findings**

Immunohistochemically, the epithelioid cells were positive for cytokeratin (AE1/AE3), synaptophysin (Syn), chromogranin A (CgA), CD56 and progesterone receptor (PR). Ganglion-like cell types showed positive reactivity for Syn and CD56. In contrast, the spindle-shaped cells showed positive reactivity for S-100. The expression of Ki-67 was extremely low (Figure 9). Bcl-2 and P53 showed negative reactivity. In addition, in case 2, numerous cells positive for CD117 scattered in the stroma (Figure 10), which indicated they were mast cells. Inversely, these cells were relatively scarce in case 1 (Figure 11). The expression pattern of these biomarkers in the metastatic tumor in lymph nodes was similar with that in the primary lesion.

**Discussion**

GP consists of three types of cells: spindle cells, ganglion-like cells and epithelioid cells [1]. Identification of the three components is essential for the diagnosis of GP. The tumor cells always arrange in solid and trabecular pattern, mainly comprising spindle cells, mixed...
Two cases report and literature review

with nests of epithelioid cells and large cells with gangliocytic differentiation [24]. Besides, other unusual structures have been reported. Huijun et al reported a case of GP with distinct glandular component embedded in the spindle tumor cells in the primary tumor and the metastatic lymph nodes [24]. Moreover, Ogata et al also found a small glandular component with mucus was present in the primary tumor and 200 cases of GP have been reported. Generally, it is regarded as a benign lesion. With the more cases of GP with regional lymph node metastasis and even distant metastasis published, the biological behavior of GP should be redefined, especially after a malignant GP of the duodenum showing a lethal course was reported by Bin et al [23]. Researchers have tried to find out some biomarkers served as prognostic indica-

Figure 9. Immunohistochemical analysis of the tumors in the duodenum. The epithelioid cells were positive for CK (A), Syn (B), CgA (C), CD56 (D) and PR (E). Ganglion-like cells showed positive reactivity for Syn (F). The spindle-shaped cells showed positive reactivity for S-100 (G). The expression of Ki-67 was extremely low (H). (A-H: Immunohistochemical staining with original magnification ×400).

200 cases of GP have been reported. Generally, it is regarded as a benign lesion. With the more cases of GP with regional lymph node metastasis and even distant metastasis published, the biological behavior of GP should be redefined, especially after a malignant GP of the duodenum showing a lethal course was reported by Bin et al [23]. Researchers have tried to find out some biomarkers served as prognostic indica-

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Two cases report and literature review

Figure 10. Immunohistochemical staining of CD117 in case 2. Numerous cells positive for CD117 scattered in the stroma (Immunohistochemical staining with original magnification ×400).

Figure 11. Immunohistochemical staining of CD117 in case 1. The cells positive for CD117 were scarce. (Immunohistochemical staining with original magnification ×400).

Bcl-2, P53 and Ki-67 were acceptable prognostic factors in several kinds of neuroendocrine tumors. However, bcl-2 and P53 showed negative reactivity in all cases of GP [1, 30]. Moreover, no matter whether lymph nodes metastases were present, Ki-67 labeling index was extremely low, even in the lethal case (less than 1% in both primary and metastatic foci) [23, 25, 30]. Similarly, we also demonstrated that the tumor cells showed negative reactivity for bcl-2 and P53 not only in the primary lesion, but also in the metastatic foci. Ki-67 positive staining was rarely present. Therefore, these biomarkers may have limited value in predicting the outcome of GP. In addition, histological features, such as necrosis or mitoses, were hardly seen in the lesion. Some authors suggested other important factors involved in the malignant process of GP and molecular techniques needed to interpret the underlying mechanisms.

Mast cells are immune cells that accumulate in the tumors and their microenvironment during disease progression. They express high levels of the tyrosine kinase receptor Kit (CD117) [31]. In vitro studies have shown that mast cells have the potential to influence many aspects of tumor biology, including tumor development, tumor-induced angiogenesis, and tissue remodeling, and the shaping of adaptive immune responses to tumors [32]. However, the contribution of mast cells to the tumor biology in vivo is still under investigation. In our two cases, we found that the presence of mast cells was more frequently in case 2 than that in case 1. We have no idea whether this is occasional owing to the limited number of cases. More cases should be recruited to elucidate the intrinsic association.

In this article, we report two cases of GP, one of which was accompanied by lymph node metastasis. The patient with lymph node metastasis has a good prognosis. Because of the metastases, close surveillance is still necessary. A long time follow-up is needed to know exactly the prognosis.

Acknowledgements

This study was conducted with the approval of the Ethics Committee of The First Affiliated Hospital, College of Medicine, Zhejiang University.

Disclosure of conflict of interest

None.

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References

Two cases report and literature review


Two cases report and literature review


