Case Report

T1 Neuroendocrine Carcinoma of Anal Canal after Transanal Resection for Intramucosal Adenocarcinoma

Hirotoshi Kobayashi1, Hideki Ueno1, Yojiro Hashiguchi1, Megumi Ishiguro1, Jiro Omata1, Yoshiki Kajiwara1, Hideyuki Shimazaki2 and Hidetaka Mochizuki1

1Department of Surgery I and 2Department of Laboratory Medicine, National Defense Medical College, Tokorozawa, Saitama, Japan

Received December 5, 2005; accepted February 6, 2006; published online May 15, 2006

Neuroendocrine carcinomas of the anal canal are rare, representing 1% of malignant tumors of the anal canal. This tumor behaves aggressively and leads to poor outcomes. The majority of tumors are found with distant metastases. We describe the case of a 63-year-old female with T1 neuroendocrine carcinoma of the anal canal arising from the site of a previous transanal excision performed 13 months earlier for intramucosal adenocarcinoma of the anal canal. The patient did not have any distant metastases on preoperative computed tomography and magnetic resonance imaging. She underwent abdominoperineal resection after the initial diagnostic transanal excision of the neuroendocrine carcinoma, which had shown submucosal invasion. No lymph node metastasis was found in pathological examination. In this case, it is likely that the neuroendocrine tumor, which infiltrated into the submucosal layer with venous invasion, had developed over the intervening 13 months following the original transanal excision of the adenocarcinoma.

Key words: anal canal - colorectal carcinoma - neuroendocrine carcinoma

INTRODUCTION

Although neuroendocrine cells are found in the gastrointestinal tract, neuroendocrine carcinomas of the colon and rectum are rare. The prognoses of patients with neuroendocrine carcinoma of the colon and rectum are worse than those of patients with adenocarcinoma (1). Anal tumors are rare tumors of the gastrointestinal tract, and neuroendocrine carcinomas represent only 1% of malignant tumors of the anal canal (2). We present a case of T1 neuroendocrine carcinoma of the anal canal which was found at the site of a previous transanal resection for intramucosal adenocarcinoma of the anal canal 13 months earlier. To our knowledge, this is the first recorded case of a neuroendocrine carcinoma arising from the site of a previous transanal resection for intramucosal adenocarcinoma of the anal canal.

CASE REPORT

A 63-year-old female was diagnosed with intramucosal adenocarcinoma (Japanese criteria) of the anal canal 7 years after transanal resection for T1 lower rectal adenocarcinoma, although she had not had a recurrence of adenocarcinoma for 7 years. Intramucosal adenocarcinoma of the anal canal, which might be diagnosed as adenoma with severe dysplasia in Western countries, was curatively resected by transanal excision (Fig. 1). Thirteen months later she underwent colonoscopy, which showed a 5 mm tumor at the edge of the scar where the previous transanal resection was performed (Fig. 2). Biopsies showed atypical cells which were different from the previous disease. On immunohistochemical staining, cytokeratin was positive and both chromogranin A and synaptophysin were equivocal.

A transanal excision of the tumor with partial inclusion of the internal anal sphincter was performed. Pathological examination showed an undifferentiated tumor composed of solid nests of small cells with minimal cytoplasm and hyperchromatic nuclei with molding (Fig. 3A). Furthermore, there were several mitoses per high-power field as well as necrotic areas within the tumor. On immunohistochemical staining, chromogranin A was positive (Fig. 4) and synaptophysin was equivocal. These findings led to the diagnosis of neuroendocrine carcinoma of the anal canal. There was atypical epithelium very close to the neuroendocrine carcinoma, although it was very difficult to diagnose it as adenoma or regenerating mucosa because of the existence of severe inflammatory reactions (Fig. 3B).

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Therefore, continuity between neuroendocrine carcinoma and adenoma was not apparent microscopically, although adenoma was observed in the specimen (Fig. 3C). Carcinoma infiltrated into the submucosal layer but not into the internal muscular layer. Venous invasion was clearly recognized (Fig. 3C). Furthermore, cancer cells reached within 1 mm of the surgical margin.

A full metastatic work-up was performed, including chest X-ray, computed tomography and magnetic resonance imaging. These examinations did not demonstrate any evidence of metastatic disease. There was no elevation of tumor markers, including carcinoembryonic antigen and CA 19-9. Abdominoperineal resection (APR) was performed because neither remnant cancer cells near the surgical margin nor nodal involvement could be assessed. Pathological examination of the final APR specimen found neither remnant cancer cells nor lymph node metastasis.

The patient did well post-operatively and was discharged home on post-operative day 16. She remains in good health 6 months after APR.

**DISCUSSION**

Anal tumors are relatively rare and represent only 5% of anorectal malignancies (3,4). Moreover, neuroendocrine carcinoma represents only ~1% of malignant tumors of the anal canal (2). Neuroendocrine carcinomas of the colon and rectum are as uncommon as those in the anal canal. Since neuroendocrine carcinoma of the colon was first described
by Gould and Chejfec (5) in 1978, the reported incidence of this tumor in the colon and rectum has varied from 0.2 to 3.9% of colorectal cancer (1,6–8). Pathologically, neuroendocrine carcinomas show solid clusters or ribbons of round to fusiform small to intermediate-sized cells with variably abundant mitoses. They are also immunohistochemically positive for chromogranin, synaptophysin or neuron-specific enolase. Electron microscopy shows dense core neuroendocrine granules in the cytoplasm of the tumor cells. It is especially important to distinguish neuroendocrine carcinoma from carcinoid tumor since their prognoses are different. Travis et al. (9) defined neuroendocrine carcinoma as having more than 10 mitoses per 10 high-power fields, as well as necrosis, neither of which is found in typical carcinoid. Moreover, in neuroendocrine carcinoma, the labeling index for Ki67 is very high, usually $>75\%$ positive nuclei (10). In the present case, several mitoses per high-power field and significant necrosis were present. Furthermore, keratin and chromogranin A were positive on immunohistochemistry.

The cellular origin of neuroendocrine carcinoma was initially postulated to be the amine precursor uptake and decarboxylation cells that migrate from the neural crest (11). However, recent experimental and clinical observations support the hypothesis that these tumors develop because of divergent differentiation of pluripotent stem cells which undergo progressive malignant differentiation under certain conditions (12). In addition, Vortmeyer et al. (13) demonstrated by genetic analyses that poorly differentiated neuroendocrine carcinoma and associated adenocarcinoma appeared to be derived from the same cell of origin, which is most likely either a pluripotent epithelial stem cell or an adenocarcinoma precursor cell. In the present case, the patient had three cancers of the lower rectum and anal canal over 8 years, although the locations of the cancers of the anal canal were the same. A previous study demonstrated that repeated mechanical injuries can enhance papillomas and carcinomas in mouse skin (14). The mechanical stimulation of transanal excision for intramucosal adenocarcinoma might influence the development of neuroendocrine carcinoma. However, we are not in favor of this theory. Especially in this case, we hypothesize that this tumor was probably derived from the residual tumor, since there were both an adenoma and a neuroendocrine carcinoma in this case. However, in the specimen resected 13 months earlier, the surgical margin was free from cancer cells and there was no evidence of an incipient neuroendocrine carcinoma.

In the present case, adenoma was present near the neuroendocrine carcinoma. The frequency of coexistence of adenoma with neuroendocrine carcinoma varied from 23 to 63\% in previous studies (Table 1) (7,15,16). Guo et al. (17) reported continuity between adenocarcinoma cells and neuroendocrine carcinoma cells. Furthermore, Yoshikane et al. (18) demonstrated a small neuroendocrine carcinoma of the rectum entirely covered by a tubulovillous adenoma. However, in the present case, the transition between the two lesions was not as clearly observed as in previous studies, although the neuroendocrine carcinoma in this case did arise from the scar of a previous transanal resection for intramucosal adenocarcinoma of the anal canal.

The majority of malignant tumors of the anal canal are squamous cell carcinomas (2). The primary therapy for patients with squamous cell carcinoma of the anal canal is chemoradiotherapy (19). However, the gold standard therapy for patients with neuroendocrine carcinoma of the anal canal is still unclear. There is difficulty in establishing this owing to the rarity of the disease. The prognosis of patients with

Table 1. Neuroendocrine carcinoma of the colon and rectum in the literature

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Frequency in colorectal cancer (%)</th>
<th>No. of cases</th>
<th>No. of patients with stage I cancer</th>
<th>Rate of co-existence of adenoma (%)</th>
<th>Rate of lymph node metastasis (%)</th>
<th>Rate of distant metastasis at diagnosis (%)</th>
<th>Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wick et al. (15)</td>
<td>1987</td>
<td>N/A</td>
<td>10</td>
<td>N/A</td>
<td>30</td>
<td>60</td>
<td>N/A</td>
<td>MS: 5M</td>
</tr>
<tr>
<td>Staren et al. (7)</td>
<td>1988</td>
<td>1.9</td>
<td>13</td>
<td>0</td>
<td>23</td>
<td>62</td>
<td>38</td>
<td>MS: 7M</td>
</tr>
<tr>
<td>Gaffey et al. (16)</td>
<td>1990</td>
<td>N/A</td>
<td>24</td>
<td>1 (4%)</td>
<td>63</td>
<td>88</td>
<td>71</td>
<td>1Y SR: 12%</td>
</tr>
<tr>
<td>Saclarides et al. (8)</td>
<td>1994</td>
<td>3.9</td>
<td>39</td>
<td>1 (3%)</td>
<td>N/A</td>
<td>79</td>
<td>39</td>
<td>6M SR: 58%, 3Y SR: 15%, 5Y SR: 6%</td>
</tr>
<tr>
<td>Bernick et al. (1)</td>
<td>2004</td>
<td>0.6</td>
<td>38</td>
<td>6 (16%)</td>
<td>N/A</td>
<td>N/A</td>
<td>65</td>
<td>1 Y SR: 46%</td>
</tr>
</tbody>
</table>

N/A, not available; MS, median survival; M, month; Y, year; SR, survival rate.
neuroendocrine carcinoma of the colon and rectum is very poor, and the 1 year survival rate has been reported to be between 12 and 15% (16,20). One of the reasons for the poor outcome is the aggressiveness of the disease. Most patients have metastatic disease at the time of diagnosis. The rate of distant metastases at the time of diagnosis is between 69 and 80% (1,21). Lymph node involvement ranges from 60 to 88% (15,16). Therefore, chemotherapy for patients with neuroendocrine carcinoma may be of importance. Since Redman et al. (22) reported a small cell undifferentiated carcinoma of the colon which responded to systemic chemotherapy, cytotoxic chemotherapeutic regimens similar to those for small cell lung cancer have been recommended. The combination of etoposide and cisplatin demonstrated a 67% response rate and a median survival of 19 months for patients with metastatic neuroendocrine tumors (23). The use of chemotherapy might contribute to the improvement of survival in patients with colorectal neuroendocrine carcinoma, of which 1 year survival has been reported to be 46% (1).

In the current case, neuroendocrine carcinoma of the anal canal was detected at a very early stage without distant and lymph node metastasis. It is uncommon to detect T1 neuroendocrine carcinoma, which has a reported frequency of 3–6% (Table 1). It is likely that this tumor did not exist 13 months earlier at the time of transanal excision of the intramucosal adenocarcinoma and that the tumor developed and infiltrated into the submucosal layer with venous invasion during the intervening period. These observations reflect the aggressiveness of neuroendocrine carcinomas. However, the best treatment for this patient seemed unclear on the basis of previous studies. After a transanal excision, radiotherapy might be the first therapeutic option. Moreover, it remains in doubt whether adjuvant chemotherapy is required for this patient with T1 neuroendocrine carcinoma. Since venous invasion was detected, surveillance for distant metastasis will be necessary. There is an urgent need to standardize treatment for such uncommon diseases as T1 anal neuroendocrine carcinoma. To achieve this, a central database that encompasses rare diseases will be necessary.

References