A metastatic G2 neuroendocrine tumor smaller than 5 mm: A case report

Manabu Inoue, Shunsuke Tsukamoto, Konosuke Moritani, Hideki Sekine, Yutaka Saito, Yukihide Kanemitsu

A R T I C L E   I N F O

Keywords:
Rectal neuroendocrine tumor
Lymph node metastasis
Robotic-assisted laparoscopic low anterior resection

A B S T R A C T

Background: Neuroendocrine tumors (NETs) measuring <10 mm are widely thought to be at low risk of lymph node metastasis. Here we report a case of lymph node metastasis in a patient with a 4-mm NET that was classified as grade 2.

Presentation of case: A 32-year-old woman was referred to our hospital after a positive fecal occult blood test. Colonoscopy revealed a 4-mm yellowish submucosal tumor, which was diagnosed as NET of the upper rectum and removed by endoscopic submucosal resection with ligation. Pathological examination of the specimen showed a 4-mm grade 2 NET with a Ki-67 labeling index of 4.4% without lymphatic or venous invasion. In accordance with the European Neuroendocrine Tumor Society guidelines, we performed robotic-assisted laparoscopic low anterior resection with lymph node dissection. Final pathological examination revealed invasion confined to the submucosal layer and metastasis to one lymph node (pT1aN1M0, Stage IIIB). There were no residual tumor cells in the scar after endoscopic submucosal resection with ligation.

Discussion: Should G2 neuroendocrine tumors smaller than 5 mm be surgically resected?

Conclusions: We encountered a rare case of a small NET with lymph node metastasis that was treated by robotic-assisted laparoscopic low anterior resection with lymph node dissection. Additional surgery is an option to be considered for grade 2 NET even if it is small because of the possibility of lymph node metastasis.

1. Introduction

Most neuroendocrine tumors (NETs) are located in the gastrointestinal tract, pancreas, or bronchopulmonary system. Rectal NETs are relatively rare and asymptomatic, representing only 1.3% of all rectal tumors. The incidence of rectal NET has been reported to be 1–1.25 per 100,000 per year [1]. However, the U.S. Surveillance Epidemiology and End Results (SEER) program has reported increases in the incidence and prevalence of NETs over the past 30 years [1]. Indeed, the incidence of rectal NETs has been increasing rapidly due to more screening colonoscopies performed and advances in radiological imaging.

The World Health Organization classification system for gastrointestinal NETs applies a grading system based on mitotic activity and the percentage of Ki-67-labeled proliferating cells (G1, G2). Poorly differentiated neuroendocrine carcinomas are classified as high-grade (G3) neuroendocrine carcinomas [2]. Although the World Health Organization has classified rectal NETs as low-grade malignant tumors, the cancer-specific survival of patients with rectal NETs and regional or distant metastasis is comparable with that of patients with rectal carcinoma.

Treatment for rectal NETs depends on tumor size, depth of invasion, and whether or not distant metastasis is present. Although the guidelines recommend endoscopic resection for rectal NETs <10 mm, there is little information in the literature regarding the frequency of metastasis of this type of tumor and no consensus regarding additional surgery for incomplete resection of rectal NETs of this size [3].

Here we report a case of a 4-mm rectal NET classified as G2 with lymph node metastasis. Although many reports have been published on rectal NETs classified as G1 due to their frequency, much less is known about the malignant potential of G2 tumors. Additional total or tumor-
specific mesorectal excision could reduce the risk of metastasis. Although lymph node metastasis is rare in patients with small NETs, the case described here highlights the importance of considering the possibility of lymph node metastasis even with tumors as small as 4 mm. This case has been reported in line with the SCARE criteria [4].

2. Presentation of case

A 32-year-old woman was referred to our hospital after a positive fecal occult blood test. She had no symptoms suggestive of a functional carcinoid tumor, such as diarrhea, flushing, or asthma-like attacks. She had no relevant family history. Her carcinoembryonic antigen level was <0.5 ng/mL and her carbohydrate antigen 19-9 level was 14 U/mL.

Colonoscopy revealed a 4-mm submucosal tumor, which was smooth, round, and slightly elevated with a yellowish discolored mucosa (Fig. 1A). The lesion was endoscopically diagnosed as NET of the upper rectum and removed by endoscopic submucosal resection with ligation (ESMR-L) (Fig. 1B–D). Computed tomography scans of the chest, abdomen, and pelvis revealed no lymph node or distant metastasis (Fig. 2A). Pathological examination showed a submucosal rectal tumor with a maximum diameter of 4 mm. Histopathological findings indicated that the tumor was composed of uniform cells with round to oval nuclei arranged in a trabecular and glandular pattern (Fig. 3A, B). The tumor was located mainly in the submucosa, and tumor cell nests were cauterized at the vertical margin (Fig. 3C). Immunohistochemically, the tumor cells were positive for synaptophysin (Fig. 3D), chromogranin, and CD56. The Ki-67 labeling index was 4.4% in the hotspot (Fig. 3E).

Robotic-assisted laparoscopic low anterior resection with lymph node dissection was performed by a surgeon experienced in robotic surgery (Fig. 2B). The operation time was 3 h 16 min and estimated blood loss was 7 mL. No swollen lymph nodes or peritoneal dissemination was found during the operation. Her postoperative course was satisfactory and she was discharged on hospital day 7.

No residual tumor cells were found at the surgical margin or in the surgically resected specimen after ESMR-L. However, lymph node metastasis of NET was detected (Fig. 3F; pT1aN1M0, Stage IIIB, according to the AJCC Cancer Staging Manual, eighth edition). The patient chose not to receive adjuvant chemotherapy but is now at least five years out from her surgery and has remained well with no signs of tumor recurrence.

3. Discussion

Most rectal NETs are small, localized, and mucosal or submucosal in location [5,6], with 66% classified as tumors with a diameter of <10 mm [7]. The overall incidence of rectal NETs is increasing rapidly in parallel with the more widespread use of screening colonoscopy and advances in radiological imaging. Given that rectal NETs can be relatively small lesions, predictors of lymph node metastasis in patients with these tumors would be clinically important.

The TNM and AJCC/UICC (eighth edition) staging systems highlight tumor size and depth of invasion as the main determinants of the prognosis of NET. Lymph node metastases have been found in 4%–18.6% of patients with NETs measuring <10 mm, 26.5% of those with NETs measuring 10–19 mm, and 60% of those with NETs >20 mm [5,8]. The frequency of metastasis of NETs with a diameter of <5 mm is still...
unclear.

According to current AJCC/UICC (eighth edition) staging, 5-year survival rates have been reported to be 92%, 88%, 59%, and 15% for stage I, II, III, and IV rectal NET, respectively. Patients with localized rectal NET have a 5-year survival rate of 98%–100% [9], while those with lymph node metastasis and distant metastasis have respective survival rates of 54%–74% and 15%–37%. Metastasis of rectal NETs could lead to survival that is as poor as that of adenocarcinoma [8]. Alongside tumor size and depth of invasion, one of the strongest risk factors for metastasis is lymphovascular invasion [9].

The noteworthy aspect of this case is that the specimen obtained by endoscopic resection in a patient with a 4-mm rectal NET classified as G2 revealed metastasis to a lymph node without lymphovascular invasion.

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The notable aspect of this case is that the specimen obtained by endoscopic resection in a patient with a 4-mm rectal NET classified as G2 revealed metastasis to a lymph node without lymphovascular invasion. According to the consensus guidelines, 3 survival is better in patients with lower-grade tumors than in those with higher-grade tumors. The ratio of G1/G2 NETs <10 mm has been reported to be 2.7% [10]. In general, a G1/2 NET that is small (<10 mm, particularly <5 mm) is considered to have a low risk of metastasis in the absence of lymphovascular invasion. However, there are some instances of lymph node metastasis in such patients, as in the present case. In fact, reports of rectal G2 NET <5 mm accompanied by lymph node metastasis are extremely rare. A search of PubMed using the keywords “rectal neuroendocrine tumor” or “rectal carcinoid” and “metastasis” identified only one report of lymph node metastasis in a patient with a G1 NET <5 mm but no G2 cases [10]. In many cases, given their small size, these tumors are assessed after endoscopic treatment to minimize the risk of metastasis.

Although there is currently no consensus regarding the management of rectal NETs <10 mm, endoscopic resection is generally the best option in the absence of lymphatic invasion. Resection can be performed using several techniques [11], among which ESMR-L is reportedly useful and safe for resection of rectal NETs ≤10 mm [11]. The R0 resection rate for ESMR-L is 95.2%. Cauterization at the vertical margin, as in our case, is rare. It is still unclear whether negative margins are necessary given the excellent outcome in patients with rectal NETs <10 mm even with positive or indeterminate margins. The positive cut end resulting from thermal ablation without lymphatic or vascular invasion after ESMR-L could technically be considered a repeat local resection according to European Neuroendocrine Tumor Society guidelines. However, in our case, we decided to perform additional radical surgery with regional lymph node dissection given that the prognosis of G2 NETs is worse than that of G1 NETs [9], even though the tumor was very small. Although the guidelines no longer recommend adjuvant chemotherapy, a recent randomized trial provides some evidence on the efficacy of peptide receptor radionuclide therapy. Tumor grade/size is an important predictor of the risk of lymph node metastasis. If a NET is small, it is difficult to assess risk based on endoscopic findings alone. Therefore, it may be better to remove specimens during biopsy or endoscopic procedures for evaluation and consider patients with G2 NET should be considered to have a high risk of lymph node metastasis. If the tumor is classified as G2, given the possibility of lymph node metastasis, additional surgery can be considered even if the tumor is small.

4. Conclusion

We encountered a rare case of a small NET with lymph node metastasis that was treated by robotic-assisted laparoscopic low anterior resection with lymph node dissection. Additional surgery can be an option for G2 NET even if it is small because of the possibility of lymph node metastasis.

Consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

Provenance and peer review

Not commissioned, externally peer-reviewed.

Ethical approval

None.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Guarantor

None.

Research registration number

None.

CRediT authorship contribution statement

None.

Declaration of competing interest

The authors declare no conflicts of interest.
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