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The primary aim of *World Journal of Clinical Cases* (*WJCC*, *World J Clin Cases*) is to provide scholars and readers from various fields of clinical medicine with a platform to publish high-quality clinical research articles and communicate their research findings online.

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Is lymphatic invasion of microrectal neuroendocrine tumors an incidental event?: A case report

Jing-Xue Ran, Liang-Bi Xu, Wan-Wei Chen, Hao-Yi Yang, Yan Weng, Yong-Mei Peng

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Abstract

BACKGROUND

A rectal neuroendocrine tumor (rNET) is a malignant tumor originating from neuroendocrine cells. Currently, tumor size is the primary basis for assessing tumor risk.

CASE SUMMARY

This article reports the case of a 46-year-old male patient who underwent a colonoscopy that found a 3 mm rectal polypoid bulge. The pathological examination of a sample collected with biopsy forceps revealed a neuroendocrine tumor. Further endoscopic submucosal dissection rescue therapy was used. The presence of lymphatic vessels indicated that the tumor had infiltrated the negative resection margin. The lesion was located in the distal rectum near the anal canal. Therefore, to ensure the patient's quality of life, follow-up observation was conducted after full communication with the patient. No tumor recurrence or distant metastasis has been found during the 13-mo follow-up after surgery.

CONCLUSION

Despite the presence of lymphatic invasion and extremely small diameter rNETs in our case, this phenomenon may not imply a higher risk of distant lymph node and organ metastasis.

Key Words: Rectal neuroendocrine tumor; Tumor size; Lymphatic invasion; Case report

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Core Tip: Due to the heterogeneity and atypical symptoms of rectal neuroendocrine tumors, in the process of clinical diagnosis and treatment, it is not sufficient to judge the risk of tumor metastasis based only on tumor size and lymphovascular invasion. Therefore, during treatment, it is necessary to formulate an individualized plan, undertake close follow-up observation, and try to improve the quality of life and disease prognosis of patients while reducing the burden of treatment.

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INTRODUCTION

A rectal neuroendocrine tumor (rNET) is a rectal malignancy that originates from neuroendocrine cells with an insidious onset and a lack of specific first symptoms[1]. In recent years, with the extensive development of colon cancer screening programs and the improvement of endoscopic diagnosis and treatment techniques, the incidence of rNET has increased annually[2]. The incidence of rNET has increased nearly 10 times in the past 30 years, indicating that this type of tumor may not be uncommon [3]. Clinically, rNETs are usually found during endoscopy, the vast majority are 10 mm or less in diameter[4]. According to the European Neuroendocrine Tumor Society guidelines, tumor size greater than 20 mm is a risk factor for tumor invasion and metastasis, but vascular invasion, lymph node metastasis, and distant metastasis may also occur in the case of smaller tumors[5,6]. Currently, for rNETs with a tumor size of 10 mm or less, existing treatment guidelines recommend radical surgery and, in the presence of definite vascular invasion, additional lymph node dissection[7,8]. Here, we report a case of a 3 mm rNET located in the distal rectum with lymphatic invasion after endoscopic resection.

CASE PRESENTATION

Chief complaints

Polypoid bulge found on colonoscopy.

History of present illness

A 46-year-old male patient underwent colonoscopy and was found to have a 3-mm-sized polypoid bulge with a smooth surface in the rectum 3 cm from the anus. After sample collection with biopsy forceps, the pathological diagnosis was neuroendocrine tumor (NET) (Figure 1).

History of past illness

No special history of past illness.

Personal and family history

The patient's father had a history of colon cancer. His Personal history has nothing notable.

Physical examination

No special.

Laboratory examinations

No special.

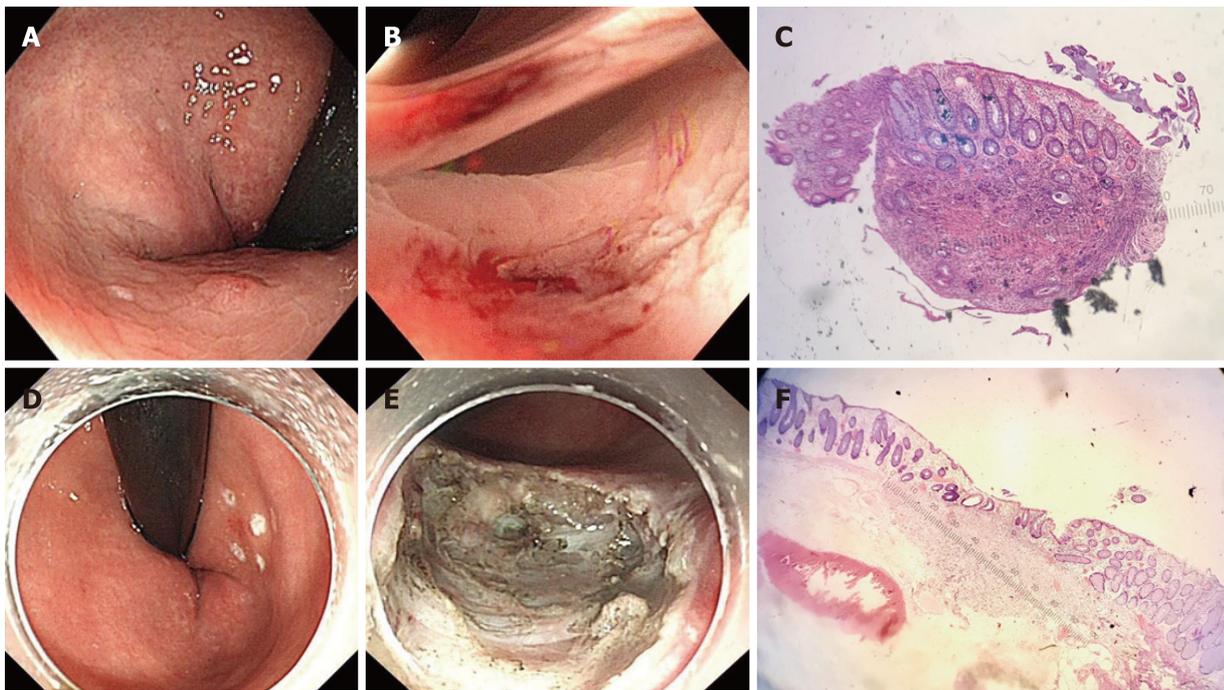
Imaging examinations

Before endoscopic submucosal dissection (ESD), computed tomography (CT) showed no abnormalities in the enhancement of the chest and abdomen.

To clarify whether additional surgery was required, further assessment by 68Gallium labeled somatostatin analogues-positron emission tomography (68Ga-SSA-PET)/CT was used, but the results showed no abnormalities.

Pathological examinations

The pathological diagnosis of the specimen after ESD rescue therapy was rNET G1. The lesion



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Figure 1 The endoscopic manifestation of the rectal neuroendocrine tumor. A-C: Rectal neuroendocrine tumor (rNET): under a white light endoscope, the surface is smooth, sessile, and the same color as the surrounding mucosa (A); after biopsy forceps (B); the first hematoxylin and eosin (H&E) stained pathological smear after the tumor was removed by biopsy forceps (C, $\times 40$). Endoscopic submucosal dissection (ESD) remedial treatment; D-F: Under white light endoscope, before ESD (D); after additional ESD (E); HE stained pathological smears of specimens after ESD (F, $\times 40$).

infiltrated into the submucosa. The depth of submucosal infiltration was 1000 μm . The distance between the deepest infiltration of the lesion and the basal incision margin was 500 μm . The lesion size was 2550 μm . The horizontal and vertical resection margins were negative (Figure 1). Immunohistochemical (IHC) results were as follows: CK (weak +), Vim (-), Syn (+), CD56 (strong +), CgA (strong +), CK7 (-), CK20 (weak +), Villin (+), CEA (focal+), and Ki-67 (2%; Figure 2). The lymphatic invasion was confirmed by D2-40 and CD31 staining (Figure 3).

MULTIDISCIPLINARY EXPERT CONSULTATION

After the pathological examination of the biopsy clamped specimen suggested neuroendocrine tumor, the patient underwent multidisciplinary consultation with oncology, surgery and nuclear medicine, and finally decided to complete ^{68}Ga -SSA-PET/CT, and no distant metastasis was found. Therefore, we decided to perform ESD after consulting the patient's consent and followed up regularly after the operation.

FINAL DIAGNOSIS

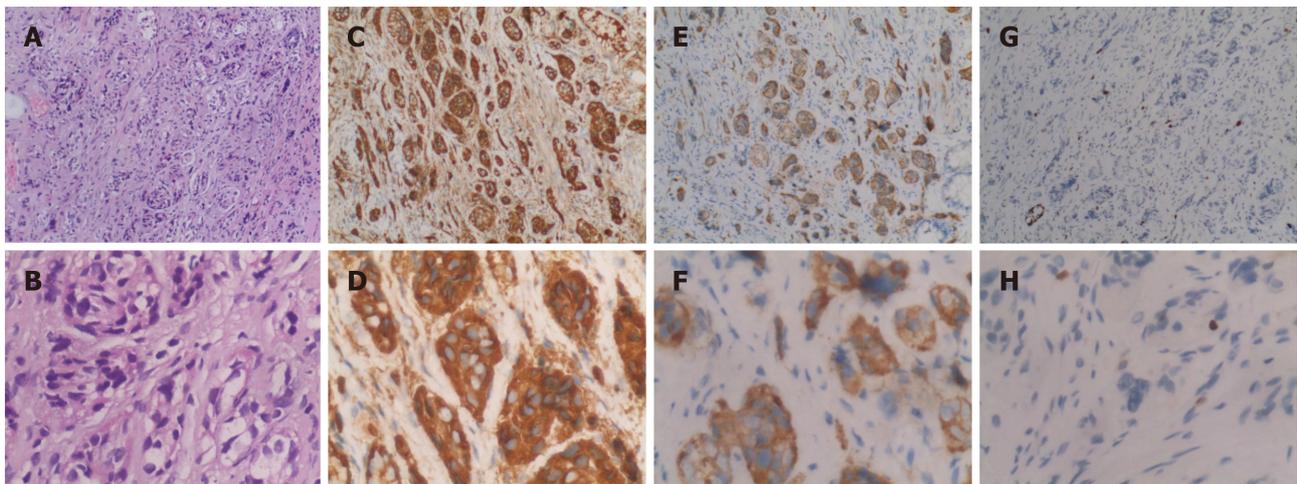
The pathological diagnosis of the specimen after ESD rescue therapy was rNET G1.

TREATMENT

ESD salvage therapy was applied.

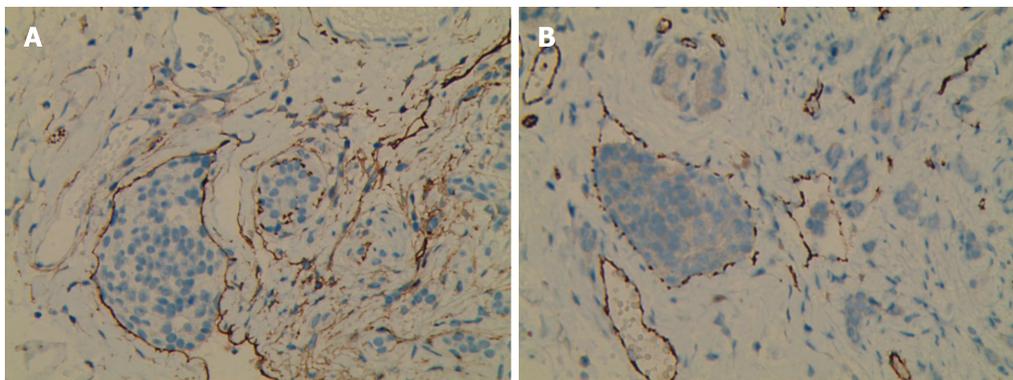
OUTCOME AND FOLLOW-UP

No tumor recurrence or distant metastasis was detected at 13 mo postoperative follow-up using endoscopy and CT-enhanced scans of the whole abdomen (including the pelvis).



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Figure 2 Pathological smears of tumor tissue after various immunohistochemical staining. A-H: HE (A, $\times 100$; B, $\times 400$); CgA (C, $\times 100$; D, $\times 400$); Syn (E, $\times 100$; F, $\times 400$); and ki67 (G, $\times 100$; H, $\times 400$).



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Figure 3 The tumor was found to have lymphatic invasion after staining with CD31 (A) and D2-40 (B). A and B: $\times 200$.

DISCUSSION

Gastroenteropancreatic neuroendocrine tumors (GEP-NETs) are the most common type of NETs[9]. The rectum is the most common site for GEP-NETs in Asian populations[10]. In recent years, with the extensive development of colorectal cancer screening programs and the improvement of endoscopic diagnosis and treatment techniques, the incidence of rNET has continued to rise.

Lymphovascular invasion (LVI) refers to the presence of tumor cells in blood vessels and lymphatic channels. LVI is closely related to tumor metastasis in distant organs and lymph nodes. A meta-analysis found that LVI was associated with an increased risk of distant lymph node metastasis (LNM) after local resection of rNETs[11]. Therefore, LVI is a risk factor for LNM. Another meta-analysis found that, for small rNETs with a tumor size of 10 mm or less, even in the presence of LVI, the prognosis was good after endoscopic resection, with a 5-year follow-up recurrence rate of only 0.3%. In addition, tiny rNETs smaller than 5 mm had a lower incidence of LVI than rNETs with a tumor size of 5-10 mm[12].

In recent years, the detection rate of LVI in rNETs has increased significantly due to immunohistochemical detection methods[12-14]. This increasing trend is proportional to tumor size, even in the fraction of rNETs less than or equal to 5 mm, the detection rate is still about 50% [13]. One study reported that the detection rate of LVI by IHC staining (56.9%) was 6 times higher than that of hematoxylin and eosin (HE) staining alone (8.8%)[15]. This result suggests that the possibility of LVI in small rNETs was underestimated prior to using IHC staining. Both vascular and lymphatic invasion are included in LVI and usually need to be distinguished by IHC detection. Vascular invasion and lymphatic invasion have different effects on LNM. In small rNETs, vascular invasion may have a greater impact on LNM than lymphatic invasion[11].

In this rNET patient, the endoscopic tumor size was 3 mm with lymphatic invasion, the smallest rNET with LVI reporting in all existing research. At the same time, no instances of LNM or distant metastasis were found after the enhanced chest and total abdominal CT and 68G-SSA-PET/CT. During

the 13-mo follow-up after ESD, we did not find tumor recurrence or distant metastasis using endoscopy at the 6-mo and 1-year postoperative follow-up. Whole abdominal CT-enhanced scans did not show tumor recurrence or distant metastasis. These findings suggest that, in small (< 10 mm) or even tiny (< 5 mm) rNETs, although there is lymphatic invasion, lymphatic invasion may not be a determinant of LNM.

A cohort study found that after 6 years of follow-up in patients with rNETs who underwent endoscopic resection, about 1% of the patients developed LNM or distant metastasis, and the tumor grades were G2. In contrast, patients with grade G1 rNETs whose tumor size was less than 20 mm and who underwent endoscopic resection did not develop lymph node or distant metastasis[16]. Therefore, the risk factors for lymph node and distant metastasis of rNETs with a tumor size less than 20 mm need further study.

Although this patient had lymphatic invasion, no lymph node or distant metastasis was found. Therefore, in the absence of a well-established correlation between LVI and LNM of rNETs with a tumor size less than 20 mm, additional surgery may not benefit all patients with LVI. The tumor grade, tumor size, LVI, and depth of invasion may still need to be comprehensively considered to determine whether to perform additional surgery. In addition, imaging studies and radionuclide scintigraphy can be considered when it is unclear whether additional surgery is required[15].

In this patient, the tumor surface was smooth, and endoscopy showed that the tumor size was small. The tumor was misdiagnosed as a hyperplastic polyp and was subjected to examination with biopsy forceps. The size of the lesion was 1500 μm . Residual lesions were found after ESD salvage surgery, in which the tumor size was found to be 1050 μm . These results indicated that simple biopsy forceps were insufficient for such rNETs, and ESD salvage was a suitable option. For hyperplastic polyps of the left colon and rectum with a tumor size of 5 mm or less, both the Japanese Society of Gastroenterology and the European Society for Gastrointestinal Endoscopy recommend endoscopic follow-up only[17,18]. The rectum is a high-incidence site of NETs. Therefore, we suggest that, if the lesions are smooth and bulging, especially when the margins of the lesions are not clear, the possibility of NETs should be considered. The possibility of NETs should be excluded by forceps and biopsy.

For this patient, to ensure his quality of life, we did not choose to conduct surgical intervention, but rather continued with follow-up observation. According to previous literature reports, the metastasis of rNETs can occur after more than 10 years[19,20]. Although no LNM and distant metastasis were found in the short-term follow-up of this patient, long-term follow-up is extremely important, especially for lymph node and liver metastasis. Therefore, this patient's end point of follow-up should be at least 10 years. In the subsequent follow-up schedule, we will perform endoscopy and CT-enhanced scans of the whole abdomen (including the pelvis) once a year, with an additional 68Ga-SSA-PET/CT if abnormalities are detected during the follow-up.

CONCLUSION

rNETs have heterogeneity and atypical symptoms. Therefore, it is not sufficient to judge the risk of tumor metastasis during clinical diagnosis and treatment based only on tumor size and LVI. Instead, during treatment, it is necessary to formulate an individualized plan, undertake close follow-up observation, and try to improve the quality of life and disease prognosis of patients while reducing the burden of treatment.

FOOTNOTES

Author contributions: Ran JX was responsible for writing the paper; Xu LB was responsible for patient treatment and study design; Chen WW and Yang HY were responsible for collecting and analyzing data; Weng Y and Peng YM were responsible for patient follow-up.

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