Comparison of characteristics between true rectal neuroendocrine tumors and rectal hyperplastic polyps among patients with endoscope-diagnosed rectal neuroendocrine tumors

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Background: To explore the white light endoscopy and endoscopic ultrasonography (EUS) features of rectal hyperplastic polyps (rHP) misdiagnosed as rectal neuroendocrine neoplasms (rNENs). In rNENs with a diameter of 5–10 mm, the endoscopic findings are not typical and some of them are similar to rHP, so it is not uncommon to misdiagnose rNENs as rHP. However, misdiagnosis of rHP as rNENs has not been reported in the literature, which can alert clinicians to the existence of this possibility and avoid over-treatment.

Methods: We collected 245 cases of rectal submucosal tumor (SMT) diagnosed by endoscopy in our hospital from January 2015 to December 2020 and 103 patients with suspected rNENs identified through endoscopy. A retrospective analysis was conducted of the shape, color, vascular dilatation, and boundary on the surface of the lesion under white light endoscope, and the source, boundary, and echo characteristics of EUS. We also analyzed the endoscopic features of rHP misdiagnosed as rNENs. Endoscopic diagnosis and pathological diagnosis were reviewed by a senior endoscopic expert and pathologist respectively. The counting data were tested and analyzed by χ^2 test and Fisher exact probability method.

Results: A total of 103 cases of rNENs were diagnosed by endoscope, among whom 75 cases were confirmed as rNENs (72.8%) and 8 cases as rHP (7.8%) by histopathology. There was no significant difference between rNENs and rHP in terms of gender, age, clinical manifestation, shape and color of lesions, dilatation of blood vessels on the surface, and location of lesions. Meanwhile, there were significant differences in whether the boundary of the lesion was clear under white light endoscopy, and the source, echo, and boundary of the lesion under EUS.

Conclusions: The morphology of some rHP is similar to rNENs under endoscopy. The boundary is clear under white light endoscopy and the source, echo, and boundary under EUS are helpful for the diagnosis of rNENs and rHP.

Keywords: Rectal neuroendocrine neoplasm (rNEN); rectal hyperplastic polyp (rHP); misdiagnosis; endoscopic feature

Introduction

Neuroendocrine tumor [NET/neuroendocrine neoplasm (NEN)] is a malignant tumor originating from neuroendocrine cells and peptidergic neurons (1). With the widespread use of high-definition endoscopy and extensive screening of colorectal cancer, the diagnosis rate of rectal neuroendocrine tumors (rectal neuroendocrine neoplasms; rNENs) is increasing. A global epidemiology study reported that the incidence rates of gastroenteropancreatic neuroendocrine tumors (GEP-NETs) are rising steadily in North America, Asia, and Europe, though this rise appears to be most profound in North America (2). Recent studies have shown that the incidence of NEN is 5.86/10,000 (3,4). According to the Surveillance, Epidemiology, and End Results (SEER) database, gastrointestinal and pancreatic NEN accounts for 58% of all NEN, of which 17.2% occur in the rectum (5,6). The incidence of age-adjusted rNENs has increased by about 10 times in the past 35 years (7)

Under white light endoscopy, lesions that display mound-like submucosal eminence, yellow penetration, hard texture, and smooth surface or ulcerated features are suspected rNENs cases. The possibility of rNENs is considered when endoscopic ultrasonography (EUS) examination shows lesions that are round or oval, hypoechoic or moderately homogeneous, with a clear boundary, and mainly originating from layer 2 (Muscularis mucosae) and/or layer 3 (Submucosa) (8). It has previously been reported that when rNENs had been suspected under endoscope, the final pathological results have shown stromal tumor, leiomyoma, lymphoma, metastatic cancer, inflammatory nodule, polyp, and so on (9,10). In general, rNENs are well differentiated small tumors with a fairly good prognosis, but they also show variations of larger tumor size, metastasis, and severe prognosis (11). A case report found that radiology of a low-grade rNEN in a 36-year-old male revealed a suspected 2.6 cm mesenteric lymph node metastasis and multiple left internal iliac lymph node metastases (12).

Rectal hyperplastic polyp (rHP) is a benign non-neoplastic disease of epithelial origin, with an incidence of about 10% (13), which is much higher than that of rNENs. Under endoscopic examination, rHP shows the same color as the surrounding mucosa or a white, smooth surface and clear boundary. Generally, rHP only needs endoscopic follow-up.

For rNENs with a diameter of 5–10 mm, the endoscopic findings are atypical and some of them are similar to rHP. According to previous reports, it is uncommon for rNENs

to be misdiagnosed as rHP, and endoscopic polypectomy most often reveals a positive basal margin and residual lesions (14-16). Similar findings have been reported in other gastrointestinal tumors. Giotis *et al.* (17) reported a case of duodenal-type follicular lymphoma in the rectum appearing as a hyperplastic polyp of duodenum and stomach, of which a similar case had never been previously reported.

However, the misdiagnosis of rHP as rNENs has not been reported in the literature in the past, but because of the collection of cases, only 8 cases were diagnosed as rHP by endoscope, the sample is relatively small, and there will be a little bias in statistics. Only this report is used to alert clinicians to the possibility of overtreatment.

In this study, we performed a review of 103 cases of endoscopic examinations of suspected rNENs in our center, of which 8 cases of rHP had been misdiagnosed as rNENs, and subsequently analyzed their endoscopic features. We present the following article in accordance with the STROBE reporting checklist (available at https://jgo.amegroups.com/article/view/10.21037/jgo-22-369/rc).

Methods

Patient population

This study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). Ethical approval and individual consent for this retrospective analysis were waived by the Ethics Committee of The Affiliated Hospital of Guizhou Medical University. We conducted a retrospective analysis (cross-sectional comparative study) of 245 cases of rectal submucosal eminence diagnosed by endoscopy in our hospital from January 2015 to December 2020.

Patients with endoscopic diagnosis of rNENs were included; the exclusion criteria were as follows: (I) postoperative pathological diagnosis of stromal tumor, lipoma, and other lesions; (II) the pathological diagnosis could not be obtained without treatment; (III) incomplete clinical data.

The extracted data included the size, shape, vasodilation, color, and boundary of the lesions under white light endoscope, and the size, source level, and echo of the lesions, and whether the boundary of the lesions was clear or not under EUS.

Preoperative evaluation methods

All patients with suspected rNENs and lesions larger than
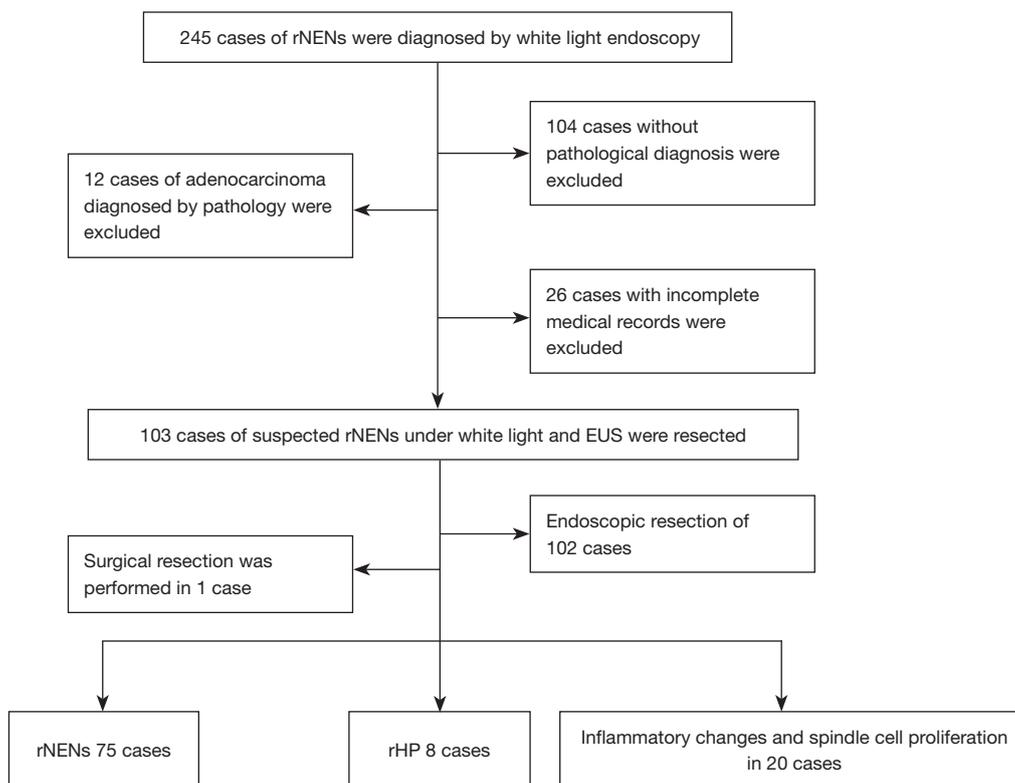
Figure 1 One hundred and three cases of rNENs diagnostic flow chart. rNENs, rectal neuroendocrine tumors; rHP, rectal hyperplastic polyp; EUS, endoscopic ultrasound.

1 cm underwent chest, abdominal, and pelvic computed tomography (CT) or B-ultrasound before operation. If there were no metastatic lymph nodes, or liver and lung metastases, endoscopic resection was performed.

Operation

A total of 103 patients underwent endoscopic or surgical resection based on the final pathological diagnosis (*Figure 1*). The rNENs endoscopic curative resection standard was employed: G1/G2, the tumor was confined to the mucous membrane and submucosa, there were no residual tumor cells at the base and horizontal cutting edge, and no lymphatic vascular invasion (14).

Pathological criteria

Pathological diagnosis was performed by a senior pathologist by review of the pathological sections of all patients. According to the rNENs pathological diagnostic criteria (18), the tumor was graded into G1, G2, and G3 according to the proliferative activity (evaluated by mitotic image number or Ki-67 positive index). Immunohistochemical (IHC) markers such as synaptophysin (Syn), chromaffin granule protein (CgA), and neuron specific enolase (NSE) were also analyzed to assist the pathological diagnosis of rNENs.

Statistical analysis

The endoscopic features of the cases were analyzed. The collected data were statistically analyzed with the software SPSS 23.0 (IBM Corp., Armonk, NY, USA). Measurement data were expressed by mean ± standard deviation ($\bar{x}\pm s$), and counting data were tested and analyzed by χ^2 test and Fisher's exact probability method. A P value <0.05 was considered statistically significant.

Table 1 Clinical features of rNENs and rHP

Clinical features	rNEN (N=75)	rHP (N=8)	χ^2	P
Gender				
Male	44	4	0.223	0.716
Female	31	4		
Clinical manifestation				
Abdominal pain & change of stool pattern	8	2	4.783	0.317
Change of stool pattern	24	1		
Hemafecia	3	0		
Abdominal pain	17	3		
Health examination	20	1		
Rests	3	1		

rNENs, rectal neuroendocrine tumors; rHP, rectal hyperplastic polyp.

Results

Overall characteristics

Among the participants, 103 cases of rNENs were diagnosed by both white light endoscopy and EUS. All cases underwent lesion resection and obtained the final pathological diagnosis. Among them, rNEN was found in 75 cases, rHP in 8 cases, and the other 20 cases displayed inflammatory changes and spindle cell proliferation (*Figure 1*). There were 44 females and 59 males with an average age of 47.18±10.57 years, and the average size of the lesion was 0.2–2.0 cm. A total of 54 cases were examined by colonoscopy because of abdominal pain, change of stool habit, hematochezia, and other focal symptoms. No carcinoid syndrome was found in all patients with rNENs. Among the 75 cases of rNENs (72.8%), G1 stage accounted for 96% (n=72) and G2 accounted for 4.0% (n=3).

Clinical features

The average age of the patients in this study was (46.84±10.75) years, and the ratio of male to female was 1.37. The clinical symptoms were not specific. Most cases showed changes in defecation habits, abdominal pain, and physical examination. There was no statistical difference in age, gender, and clinical manifestations between the 2 groups. The details are shown in *Table 1*.

Endoscopic features

Among the 75 cases of pathologically confirmed rNENs, distribution in the lower half of the rectum (≤10 cm) was the most common (94.7%), with a diameter of 0.2–2.0, most of them were within 1.0 cm (93.3%), and 6 cases were greater than 1.0 cm; the pathological grade was G1 (n=72, 75.96%), endoscopic resection was performed in 74 cases, and surgical resection was performed in 1 case.

During the follow-up period from endoscopic therapy to December 2020, all 75 cases survived without recurrence or metastasis. The endoscopic manifestation is shown in *Figure 2*.

A total of 28 cases were misdiagnosed. The endoscopic findings of misdiagnosed rHP are shown in *Table 2* and *Figure 3* below. The final pathological results of misdiagnosed cases were rHP 8 (n=8), chronic inflammatory change (n=13), spindle cell hyperplasia (n=4), and rectal tubular adenoma (n=3).

There was no significant difference between rNENs and rHP in terms of gender, age, clinical manifestation, shape and color of lesions, dilated vessels on the surface, and location of lesions under white light endoscope; there were significant differences in whether the boundary of lesions was clear under white light endoscopy, the origin and echo of lesions under EUS, and whether the boundaries were clear or not (*Table 3*).
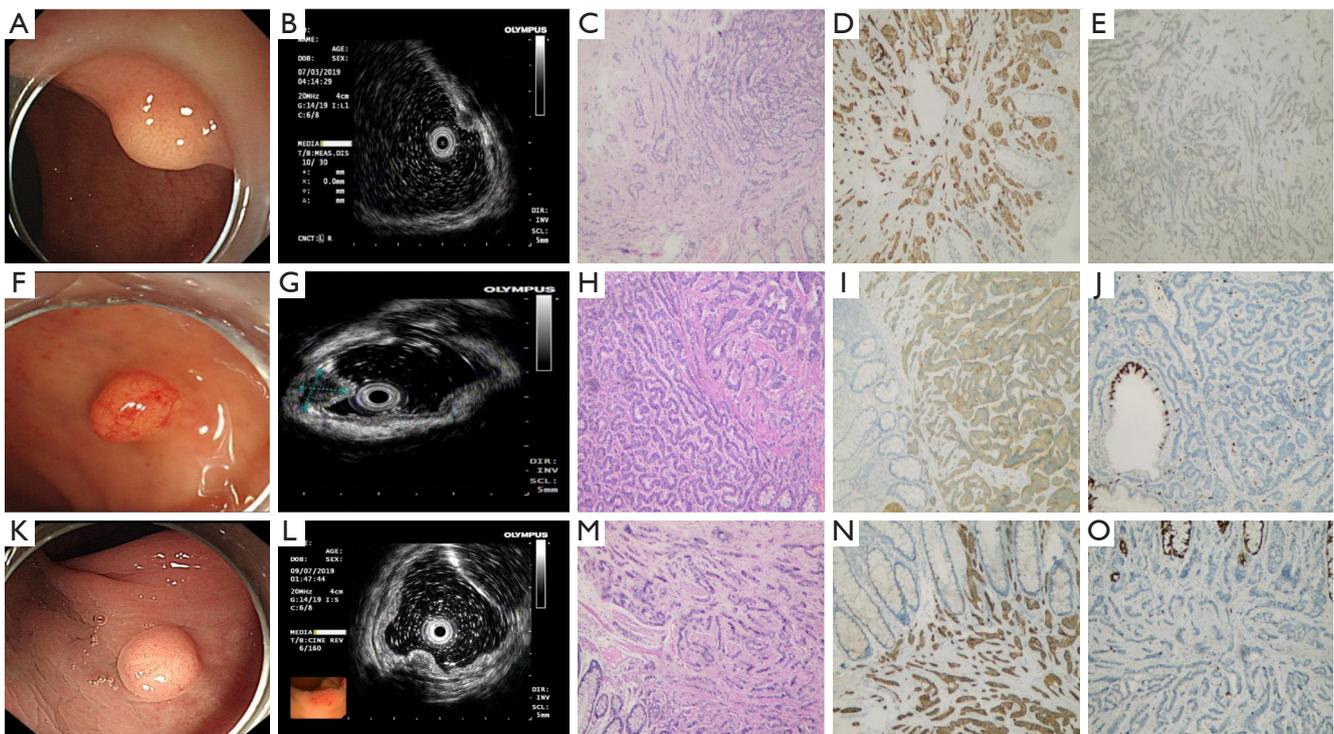
Figure 2 The endoscopic manifestation of rNENs in different stage. (A-E) G1 rNENs: the white light endoscope shows protuberance, yellow and white, and the boundary is not clear. EUS indicates that it originates from layer 2, low echo, homogeneous echo and well-defined mass. C, D and E were stained by HE, Syn, and ki67 respectively, ×40. (F-J) G2 rNENs: the white light endoscope showed protuberance, red color, a large number of dilated blood vessels on the surface, and the boundary was unclear. Under EUS, originated from the second layer of hypoechoic clear mass, H, I, J were stained under HE, Syn, and ki67 respectively, ×40. (K-O) G1 stage rNENs: White light endoscopy showed protuberance, gray, a small amount of dilated blood vessels on the surface, clear boundary. EUS suggested that the boundary was clear from layer 2, and the low echo was uniform. M, N and O were stained by HE, Syn, and ki67 respectively, ×40. rNENs, rectal neuroendocrine tumors; rHP, rectal hyperplastic polyp; HE, hematoxylin and eosin; EUS, endoscopic ultrasound.

G2 rNENs and rHP

There was no correlation between G2 rNENs and rHP, as shown in *Table 4*. Under white light endoscope, there are a large number of dilated blood vessels on the surface of rNENs compared with those in rHP, G2, as shown in *Figure 4*.

Discussion

According to the guidelines of the European Society of Neuroendocrine Oncology and the consensus of China (17,19,20), preoperative evaluation of rNENs is essential. White light endoscopy combined with EUS can evaluate the size of the tumor, the depth of invasion, and the existence of lymph node invasion to determine the appropriate follow-up treatment. At the same time, it is suggested to implement abdominal CT and pelvic magnetic resonance imaging (MRI) examination to exclude metastasis. At present, in the treatment of rNENs, endoscopic resection is performed when the diameter is less than 1 cm, the lesion is limited to mucosa and submucosa, and there are no other high-risk factors. Endoscopic treatment can be considered when the lesions are under 2 cm.

Endoscopic rNENs have certain characteristics (21), usually displaying hemispherical or mound-shaped wide base eminence, yellowish or grayish white, clear boundaries, hard texture of biopsy forceps, smooth surface mucosa, and visible capillaries. An EUS can evaluate the primitive layer, internal parenchyma echo uniformity, and lesion echo of submucosal tumors (SMT) (22). Most of them are situated

Table 2 Endoscopic features of rHP in 8 cases

Case	White light endoscopy					EUS		
	Diameter (cm)	Shape	Superficial vascular proliferation	Color	Boundary	Layer	Echo	Boundary
1	0.6×0.4	Flat	No	Yellowish White	Unclear	1, 2	Hypo	Unclear
2	0.7×0.8	Hump	Yes	Yellowish White	Part of visible	1, 2	Medium	Clear
3	1.0×1.0	Arch	No	Yellowish White	Part of visible	1, 2	Hypo	Clear
4	0.8×0.5	Flat	No	Yellowish White	Part of visible	2	Hypo	Unclear
5	0.5×0.4	Flat	No	Yellowish White	Part of visible	1, 2	Medium	Unclear
6	0.5×0.6	Hump	No	Red	Unclear	1, 2	Medium	Clear
7	0.5	Hump	No	Yellowish white	Part of visible	1, 2	Medium	Clear
8	0.5	Flat	Yes	Yellowish white	Unclear	2	Hypo	Unclear

rHP, rectal hyperplastic polyp; EUS, endoscopic ultrasound.
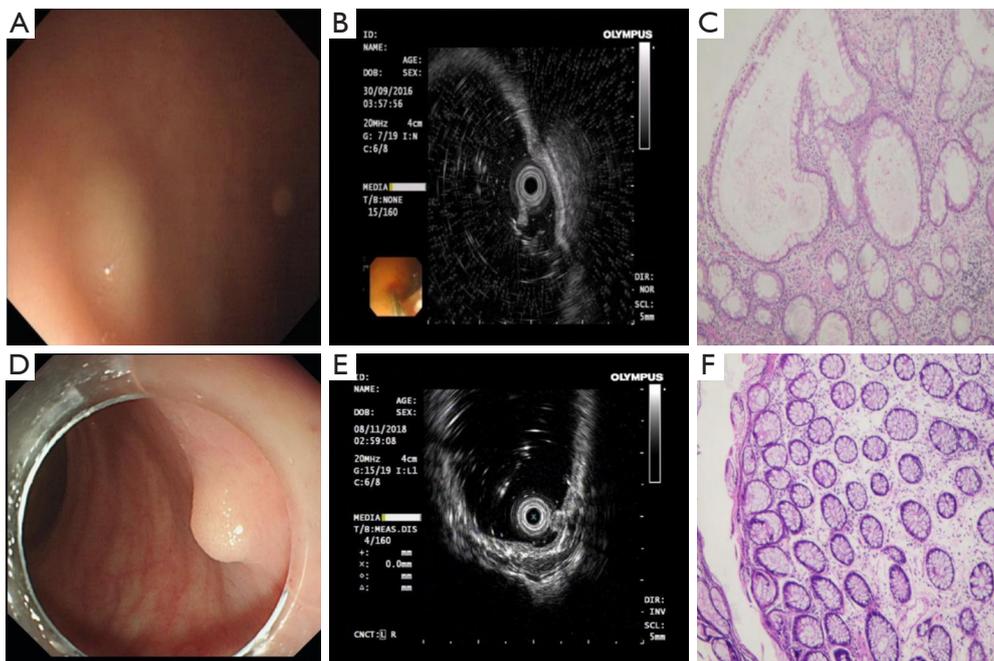
Figure 3 The endoscopic manifestation of rHP. (A-C) rHP: under white light endoscope, flat, yellow and white, the boundary is not clear; EUS: layer 1 and 2, hypoechoic, unclear boundary mass, C: HE, ×40. (D-F) Under white light endoscope it was a hump, whitened- color, with a visible lesion at the border, EUS: layer 1 and 2 hypoechoic, well-defined mass, F: HE, ×40. rNENs, rectal neuroendocrine tumors; rHP, rectal hyperplastic polyp; HE, hematoxylin and eosin; EUS, endoscopic ultrasound.

Table 3 Comparison of endoscopic findings of rNENs and rHP

Endoscopy	Characteristic	Feature	rNEN (N=75)	rHP (N=8)	χ^2	P value
White light endoscopy	Shape	Flat	41	4	0.533	0.874
		Hump	27	3		
		Arch	7	1		
	Color	Red	1	1	3.646	0.218
		The same	9	0		
		Yellowish white	65	7		
	Superficial vascular proliferation	Yes	26	2	0.302	0.711
		No	49	6		
	Boundary	Clear	8	0	10.248	0.006
		Part of visible	8	5		
		Unclear	59	3		
	From the anus	Low	18	2	5.567	0.063
		Middle	53	4		
		High	4	2		
EUS	Layer	1	1	0	12.445	0.004
		2	60	2		
		1&2	13	6		
		2&3	1	0		
	Echo	Hypo	71	4	16.559	0.002
		Medium	4	4		
	Boundary	Clear	63	0	5.370	0.041

rNENs, rectal neuroendocrine tumors; rHP, rectal hyperplastic polyp; EUS, endoscopic ultrasound.

in the first and/or second and third layers of the lesion source, with low or medium-low echo, uniform internal echo, and clear boundary, which is consistent with the results of this study.

In this study, 8 cases of rHP were misdiagnosed as rNENs, all of which were located in the middle and low rectum, the color was yellow or white under white light endoscope, and the boundaries were unclear. The EUS showed that they mostly originated from layer 1 and 2 and were hypoechoic; 4 cases had clear boundaries, which was very similar to that of rNENs, and was the cause of endoscopic misdiagnosis.

In a Korean study, it was reported that the diagnosis rate of rNENs in colonoscopic screening was 0.17%, which was much lower than the incidence of adenomas and hyperplastic polyps (23). Most rNENs showed small,

round, smooth, polyp-like protuberances covered with normal mucosa, which made it difficult to differentiate from other colorectal polyps (24-26). Between 80% and 92% of rNENs had a diameter of <1 cm at the first endoscopic diagnosis (25), which made misdiagnosis or even missed diagnosis easy because of the small lesion size. Cha *et al.* reported that 9.3% of rNENs were misdiagnosed as polyps and endoscopic mucosal resection (EMR) resulted in residual lesions (27).

There has been no previous report of rHP misdiagnosed as rNENs. Also known as metaplastic polyp, rHP is a common benign non-tumor proliferative polyp displaying single or multiple, endoscopic gray-white or homochromatic, well-defined polyps. None of the 8 cases of rHPs reported in this paper had a completely clear boundary, and EUS detected that they originated from

Table 4 Endoscopic features of rNENs and rHP in G2

| Endoscopy	Characteristic	Feature	G2 (N=3)	rHP (N=8)	χ^2	P value
White light endoscopy	Shape	Flat	0	4	3.000	0.273
		Hump	3	3		
		Arch	0	1		
	Color	Red	1	1	1.727	0.491
		Yellowish white	2	7		
	Superficial vascular proliferation	Yes	3	2	4.950	0.061
		No	0	6		
	Boundary	Part of visible	0	5	3.438	0.182
		Unclear	3	3		
	From the anus	Low	0	2	1.727	0.491
		Middle	3	4		
		High	0	2		
EUS	Layer	2	2	2	4.950	0.061
		1&2	0	6		
		2&3	1	0		
	Echo	Hypo	3	4	2.357	0.236
		Medium	0	4		
	Boundary	Clear	3	4	2.357	0.236
		Unclear	0	4		

rNENs, rectal neuroendocrine tumors; rHP, rectal hyperplastic polyp; EUS, endoscopic ultrasound.

layers 1 and 2, which may be related to the mode of growth.

In this study, it was found that part of the rHP has a smooth surface, the boundary is not clear, and the EUS came from the first or second layer, so care must be taken to distinguish it from rNENs. Cha JH, (27) asserted that rNENs suspected by endoscope should be biopsied before endoscopic resection. However, the opinions of researchers differ regarding whether rNENs should be biopsied or not. Meriam et al. (15) contemplated that preoperative biopsy was the reason lesions could not be removed completely under endoscope, so they proposed that for the lesions suspected of rNENs, preoperative biopsy should not be performed, but EMR or endoscopic submucosal dissection (ESD) should be performed directly. Since the size of rNENs focus is small, and most of the tumors are located in the deep layer of mucosa or submucosa, some endoscopic biopsies are superficial, making it difficult to obtain pathological results with diagnostic value, which can easily lead to misdiagnosis and missed diagnosis (28).

Due to its good prognosis, rHP can be followed up without endoscopic resection. Endoscopic resection may lead to misdiagnosis as rNENs, which not only increases the medical cost, but also the risk of complications. Therefore, preoperative diagnosis is particularly important. A total of 8 cases of rHP were misdiagnosed as rNENs I this study, the main causes of which were yellow and white appearance under endoscope and unclear boundary. Therefore, we believe that biopsy is meaningful when it is difficult to differentiate, and lesions of rHP and other epithelial sources can be excluded. With the progress of endoscopic technology, adhesion after biopsy has little effect on follow-up endoscopic resection.

From reviewing these misdiagnosed cases, we can draw some experiential conclusions: (I) rNEN is the most common clinical submucosal eminence of rectum, and the endoscopic findings of most cases are similar to rHP and lead to a more subjective diagnosis. (II) the boundary of the lesion should be carefully observed, especially when it
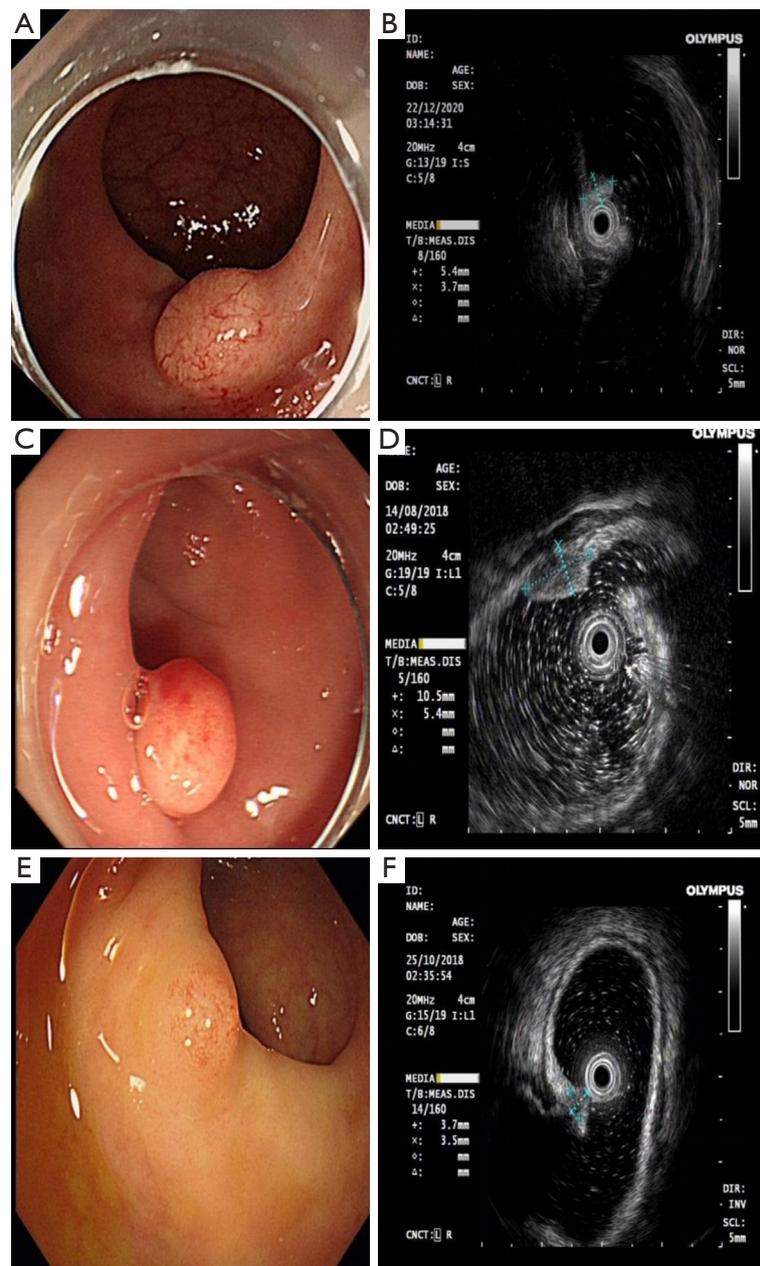
Figure 4 Endoscopic similarities between rHP and G2 rNENs. (A) G2 rNENs: a large number of dilated blood vessels can be seen on the surface under white light endoscope, (C,E) rHP: erythema or a little dilated blood vessels can be seen under white light endoscope. B, D, and F are endoscopic ultrasound images corresponding to A, C and E respectively. rNENs, rectal neuroendocrine tumors; rHP, rectal hyperplastic polyp; EUS, endoscopic ultrasound.

is found that part of the boundary is clear. For example, of the 8 cases of rHP in this study, partial boundaries could still be seen in 5 cases, and biopsy is feasible when it is difficult to differentiate. (III) the experience and operation of endoscopists are also related to the accuracy of diagnosis.

This study included 3 cases of G2 stage, whether there were dilated blood vessels on the lesion surface under white light endoscope, and there was no statistical significance between the source level of EUS. Due to the small number of samples included, further study is needed.

This was a retrospective single-center study, with some limitations: the number of study cases was small, which may have affected the results. In future, a large sample, multi-center, prospective study is needed to verify the above conclusions.

Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://jgo.amegroups.com/article/view/10.21037/jgo-22-369/rc

Data Sharing Statement: Available at https://jgo.amegroups.com/article/view/10.21037/jgo-22-369/dss

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jgo.amegroups.com/article/view/10.21037/jgo-22-369/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). Ethical approval and individual consent for this retrospective analysis were waived by the Ethics Committee of The Affiliated Hospital of Guizhou Medical University.

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