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Endoscopic features of rectal mucosal prolapse syndrome (RMPS): Differentiation from malignant rectal tumor

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ABSTRACT

Background and study aims Rectal mucosal prolapse syndrome (RMPS) usually manifests as rectal bleeding and tenesmus. Endoscopically it can be easily misdiagnosed as malignant rectal tumor (MRT). This study aimed to investigate factors to distinguish RMPS and MRT and to explore endoscopic features of RMPS.

Patients and methods Data from patients endoscopically diagnosed with rectal lesions, masses, or tumors, were retrospectively collected. Clinical information, endoscopic images, and histologic reports were reviewed. Patients endoscopically and histologically diagnosed with RMPS were included for phenotype classification.

Results 826 patients were enrolled, among them 755 (91.4%), 22 (2.7%), 10 (1.2%), and 39 (4.7%) were respectively diagnosed with MRT, RMPS, endometriosis, and neuroendocrine tumors. Compared with MRT, patients with RMPS were significantly younger (33.5 vs. 62, $P < 0.001$) and lesions were significantly smaller (2 cm vs. 3 cm, $P = 0.007$). Moreover, the clinical course of patients with RMPS was significantly longer than for those with MRT (12 months vs. 3 months, $P < 0.001$). Morphologically, we classified lesions of RMPS into five phenotypes, that is, lesions with circumferential stenosis (19.4%), protrusions (41.7%), both ulcers and protrusions (11.1%), ulcers (11.1%), and flat manifestations (16.7%). Protruding lesions were more frequently observed in females ($P = 0.039$), whereas ulcerative lesions were found involving a smaller proportion of the rectal circumference ($P = 0.028$). Lesions with only ulcers were found with a shorter distance compared with those with only protrusions (5 cm vs. 10 cm, $P = 0.034$).

Conclusions Age, clinical course, and size of the lesion can be applied to distinguish MRT and RMPS. Five phenotypes have been identified and features of ulcers/protrusions should be further explored.

Introduction

Rectal mucosal prolapse syndrome (RMPS) is regarded as a dislocation between the muscular layer and the mucosa, leading to protrusion of rectal mucosa into the cavity and an abnormality of defecation. Generally, RMPS includes rectal mucosal prolapse, solitary rectal ulcer syndrome (SRUS), inflammatory cloacogenic polyp, and colitis cystica profunda (CCP) [1], and the estimated prevalence of RMPS has reached more than 1 per 100,000 person-years [2]. Currently, it has been widely accepted that long-term intra-abdominal hypertension, chronic illness-related malnutrition, developmental abnormality, and neuro-endocrine disorder mainly contribute to ischemia of the

rectal mucosa, together with weakness and weakness of pelvic floor muscles, resulting in detachment, prolapse, and even necrosis of the mucosa [3, 4]. Patients with RMPS mostly complain about rectal bleeding, abdominal pain, incontinent defecation, and constipation [5, 6, 7]. Correspondingly, patients are educated to change their diet and improve defecation habits, treated with glucocorticoids or sulfasalazine, and even receive endoscopic or surgical interventions [2, 8, 9].

Endoscopically, RMPS manifests as ulcerative, polypoidal or nodular, or erythematous rectal mucosal lesions, commonly located on the anterior or anterolateral rectal wall [10]. The disease can be easily mistaken for a malignant rectal tumor (MRT), or inflammatory bowel disease (IBD), whereas the clinical management and long-term prognosis varies greatly. Furthermore, RMPS is still unfamiliar to clinical physicians, delaying diagnosis and making clinical management challenging [1].

To better distinguish RMPS with MRT, endometriosis, and neuroendocrine tumor (NET), our study retrospectively collected data about patients endoscopically described as having a "rectal lesion," "rectal mass," or "rectal tumor" and about their final pathology reports. We compared the epidemiology of these diseases and explored possible predictive factors favoring RMPS instead of MRT. Interestingly, we further classified endoscopic manifestations of RMPS into five types and explored whether there is any possible clinical significance of each type.

Patients and methods

Study design and patient selection

We retrospectively collected data from patients who were hospitalized in the First Affiliated Hospital of Sun Yat-sen University between January 1, 2020 and October 1, 2023, and who were endoscopically diagnosed with a "rectal lesion," "rectal tumor," or "rectal mass". Inclusion criteria were as follows: 1) the patient involved must receive at least one routine colonoscopy in our hospital; 2) "rectal mass," "rectal lesion," or "rectal tumor" was involved in the endoscopic diagnosis; 3) at least one biopsy was taken, and it was pathologically and clinically regarded as "rectal mucosal prolapse," "rectal carcinoma," "endometriosis," or "neuroendocrine tumor"; and 4) the patient had no rectal prolapse outside the anus. Exclusion criteria were as follows: 1) rectal prolapse beyond the anus was observed; 2) the tissue was pathologically described with terminology such as "chronic mucosal inflammation," "tubular adenoma," "inflammatory polyp," or "metastasis".

To further explore phenotypes of rectal mucosal prolapse under routine colonoscopy and their clinical significance, we included patients from Union Hospital, Tongji Medical College, Huazhong University of Science and Technology between June 2015 and December 2019, following the previously described inclusion and exclusion criteria.

Ethical guidelines from the 1975 Declaration of Helsinki were strictly followed during our study. Individual information has been carefully de-identified.

Equipment and technique procedures

Routine colonoscopy (CV-290 [Olympus Corporation, Japan], VP-7000 [Fujifilm Corporation, Japan]) was performed by endoscopists who had more than 3 years of clinical experience. Colorectal mucosa was carefully examined and imaged. Abnormal lesions all received biopsy for further pathologic examination.

Definitions

Patients who were pathologically confirmed as having "mucosal prolapse," "solitary rectal ulcer," or "inflammatory cap polyposis," and clinically approved as "rectal mucosal prolapse" by endoscopists were eventually classified into the RMPS group. Those with pathology described as "adenocarcinoma," "squamous cell carcinoma," or "high-grade intraepithelial neoplasia" were classified into the "rectal carcinoma" group. "Dirty exudations" referred to lesions covered with necrotic tissues, instead of feces, bacterial metabolites, or foreign materials.

Data collection

Demographic information (age and gender), clinical manifestations (symptoms and course) and endoscopic features (size of the lesion [the max diameter], distance from the lesion to the anus, ratio of the lesion to the rectal circumference, circular lesion or not, dirty exudation or not, polyp or not) were collected. Images were reviewed by two experienced endoscopists. Variables with missing values greater than 20% were not included in the statistical analysis.

Statistical analysis

Categorial variables including gender, clinical symptoms (including constipation, rectal bleeding, mucous stool, and pain during defecation), circular lesion, dirty exudation, and polyp are presented as "absolute value (ratio)". Correspondingly, continuous variables following normal distribution are expressed as "mean (standard deviation)," while those not are organized as "median (interquartile range)". The Shapiro-Wilk test was used for normality testing. An independent sample *t*-test was used to determine differences in data following normal distribution. Similarly, the Mann–Whitney U test was applied for those not following normal distribution. Chi-square/Fisher's exact test was applied to determine significant associations between categorical variables. Variables with $P < 0.10$ in the univariate analysis were included for further multivariate analysis. Logistic regression analysis was applied. A Box-Tidwell model was used to check the linear relationship among continuous independent variables and the dependent variable. Receiver operating characteristic curve and restricted cubic spline with four knots were used for transformation of continuous variables into ordinal categorical variables. Collinearity was considered in case of either tolerance < 0.1 or variance inflation factor > 10. A two-tailed $P < 0.05$ was defined as statistically significant. IBM SPSS Statistics software (version 25.0, IBM Corp, Armonk, New York, United States) and R software (version 4.2.1) was used for statistical analysis.

▶ **Table 1** Distribution of RMPS, MRT, endometriosis, and NETs in patients endoscopically diagnosed with "rectal mass" OR "rectal lesion" OR "rectal tumor".

	MRT	RMPS	Endometriosis	NET
2020	148	3	2	6
2021	145	7	2	5
2022	207	9	4	12
2023	255	3	2	16
Total	755	22	10	39
Proportion	0.914	0.027	0.012	0.047

MRT, malignant rectal tumor; RMPS, rectal mucosal prolapse syndrome; NET, neuroendocrine tumor.

Results

Epidemiology

We collected data from 826 patients who received a white-light colonoscopy examination and were endoscopically diagnosed with "rectal mass" OR "rectal lesion" OR "rectal tumor" from January 1, 2020 to October 1, 2023. Among them, with the confirmation of pathologic biopsy, 755 patients (91.4%) were diagnosed with MRT, while 22 (2.7%), 10 (1.2%), and 39 (4.7%) were confirmed with rectal mucosal prolapse (RMP), endometriosis, and NET, respectively (▶ **Table 1**). Among patients diagnosed as having MRT, high-grade intraepithelial neoplasia accounted for 11.0% (83/755). More specifically, with no infiltration beyond the submucosa layer, early-stage rectal carcinoma accounted for 76.8% of cases (580/755).

Differentiation with MRT

Because clinical management and prognosis of MRT and RMP differ greatly, we further explored whether there were epidemiological or morphologic characteristics that better distinguished these two diseases. (▶ **Table 2**)

From the view of epidemiology, patients with MRT were significantly older than those with RMP (MRT group: median 62.0 years old; RMP group: median 33.5 years old; $P < 0.001$), while the clinical course of MRT patients was significantly shorter compared with that in patients with RMP (MRT group: median 3 months; RMP group: median 12 months; $P < 0.001$). However, not significant variation in gender was seen ($P = 0.676$).

Under white-light colonoscopy examination, lesion size was found to be significantly larger in the MRT group, with a median diameter of 3 cm in the that group versus 2 cm in the RMP group ($P = 0.007$). Moreover, ratio of lesion to rectal circumference in the MRT group significantly exceeded that in the RMP group (MRT group: mean 0.531; RMP group: mean 0.303; $P = 0.014$). Similarly, circular lesions (more than half the circumference) were more frequently observed in patients with MRT (MRT group: 69.8%; RMP group: 36.4%; $P = 0.001$). Last but not least, dirty exudation was more frequently described in the MRT group compared with the RMP group (MRT group: 24.2%; RMP group: 4.5%; $P = 0.032$). Interestingly, distance from lesion to anus, and the proportion of polyp did not differ significantly in these two groups ($P = 0.423$, and 0.386 respectively). In multivariable analysis, we further observed that patients younger than 47 years old were more significantly likely to suffer RMPS instead of MRT compared with those who were older ($P = 0.005$). In addition, lesions diameter exceeding 1.1 cm and clinical course shorter than 5.5 months significantly supported the diagnosis of MRT rather than RMPS (size: $P = 0.022$; course: $P = 0.038$). In subgroup analysis, compared with patients with high-grade intraepithelial neoplasia, those with RMPS were younger, had a longer clinical course, and their lesions were smaller, although the differences were not statistically significant (▶ **Table 3**).

We further explored whether there was any factor that correlated with infiltration depth to help distinguish RMPS from rectal carcinoma. Age was always an important factor regardless of infiltration depth of carcinoma (RMPS vs. MRT infiltrating muscularis mucosa, mean, 38.59 vs. 65.22, $P < 0.001$; RMPS vs. MRT infiltrating submucosa, median, 33.5 vs. 50, $P = 0.005$; RMPS vs. MRT infiltrating muscularis propria, mean, 38.59 vs. 63.53, $P < 0.001$; RMPS vs. MRT infiltrating serosa, mean, 38.59 vs. 62.9, $P < 0.001$; RMPS vs. MRT breaking serosa, mean, 38.59 vs. 57.92, $P = 0.002$). Besides lesion size, distance

▶ **Table 2** Clinical and endoscopic features of patients diagnosed with either RMPS or MRT.

Variable	MRT	RMP	*P* value	Adjusted *P* value
Lesions size (median, cm)	3	2	0.007	**0.029**
Distance from lesion to anus (median, cm)	10	9	0.423	
Ratio of lesion to the rectal circumference (mean)	0.531	0.303	0.014	0.453
Circular lesion or not (proportion)	69.8%	36.4%	0.001	
Dirty exudation or not (proportion)	24.2%	4.5%	0.032	0.998
Polyp or not (proportion)	45.7%	36.4%	0.386	
Age (median, years)	62	33.5	<0.001	**0.003**
Gender (female, proportion)	36.2%	31.8%	0.676	
Clinical course (median, months)	3	12	< 0.001	**0.015**

MRT, malignant rectal tumor; RMPS, rectal mucosal prolapse syndrome.

▶ **Table 3** Clinical and endoscopic features of patients diagnosed with either RMPS or high-grade intraepithelial neoplasia.

Variables	RMPS	High-grade intraepithelial neoplasia	*P* value	Adjusted *P* value
Lesion size (median, cm)	2	3	**0.007**	0.976
Distance from lesion to anus (median, cm)	8	10	0.166	
Ratio of lesion to rectal circumference (median)	0	0.5	0.108	
Circular lesion or not (%)	36.4	61.4	**0.035**	0.982
Dirty exudation or not (%)	4.5	18.1	0.216	
Polyp or not (%)	36.4	54.2	0.136	
Age (mean, years)	38.59	62.53	**< 0.001**	0.978
Gender (female, %)	31.8	37.3	0.631	
Course (median, months)	12	4.5	**0.038**	0.987

MRT, malignant rectal tumor; RMPS, rectal mucosal prolapse syndrome.

from lesion to anus and ratio of lesion to rectal circumference also were significantly different between patients with RMPS and those with MRT infiltrating serosa (size, mean, 2.092 cm vs. 3.833 cm, $P = 0.018$; distance, mean, 7.733 cm vs. 11.143 cm, $P = 0.001$; ratio, median, 0 vs. 0.67, $P = 0.002$).

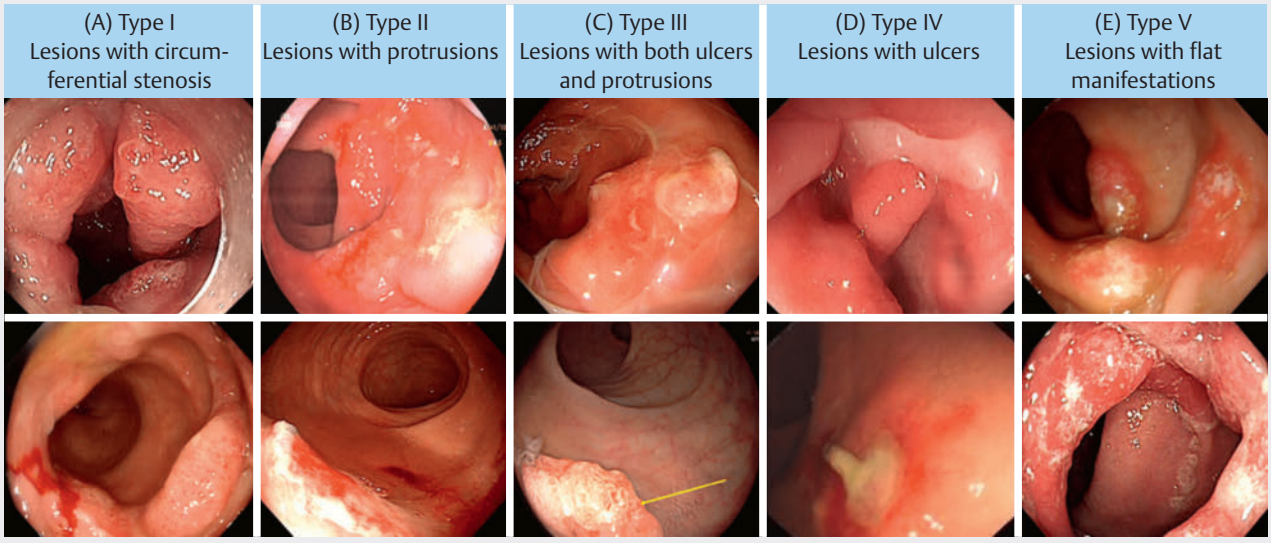
Morphologic phenotypes of RMPS

Morphologically, we further collected data from patients diagnosed with RMP from Union Hospital, Tongji Medical College and eventually classify their RMP lesions into five types according to gross appearance. Seven patients (7/36, 19.4%) suffered RMP with lesions with circumferential stenosis, manifested as circular thickening and protrusion involving more than half of the rectal circumference, contributing to a narrow rectal cavity. Lesions with protrusions were seen in 15 patients (15/36, 41.7%), which manifested as scattered polyps or nodules on the rectal mucosa instead of circular distribution. Lesions with both ulcers and protrusions were seen in four patients (4/36, 11.1%), who had both ulcerative and polypoidal/nodular lesions on the mucosa. Four patents (4/36, 11.1%) had lesions with ulcers, or RMP with mainly ulcerative lesions on the rectal mucosa. Lesions with flat manifestations with seen in seven patients with RMP (6/36, 16.7%), which manifested as hyperemia and edema of the rectal mucosa without any ulcerative or protruding phenotypes. Typical endoscopic images of these five types are shown in ▶ **Fig. 1**. Interestingly, we found that RMPS manifesting as protrusions (including Type I, II, and III) was less common in males (57.7% vs. 100%, $P = 0.039$), whereas RMPS with ulcers (including Type III, and IV) was observed with less involvement of the rectal circumference (median, 0% vs. 100%, $P = 0.028$). On the other hand, compared with groups with merely protrusions, in those with only ulcers, they were a shorter distance from the anal verge (median, 5 cm vs. 10 cm, $P = 0.034$) (▶ **Table 4**).

Discussion

Our study retrospectively explored epidemiology of RMP, rectal carcinoma, endometriosis, and NET among patients endoscopically described as having a "rectal mass," "rectal tumor," or "rectal lesion," underscoring that the MRT group accounted for 91.4% and RMPS only 2.7% of cases. Compared with lesions of MRT, those diagnosed as RMP usually had smaller diameters. Furthermore, patients with MRT were significantly older and had a notably shorter clinical course. Interestingly, we classified lesions of RMPS into five types according to their morphology under white-light colonoscopy, that is, lesions with circumferential stenosis, lesions with protrusions, lesions with both ulcers and protrusions, lesions with ulcers, and lesions with flat manifestations. We found that protruding lesions were more frequently observed in females while those with ulcers were further away from the anus.

To date, many studies have been performed involving the epidemiology, clinical manifestations, and endoscopic features of RMPS. Clinically, rectal bleeding, tenesmus, constipation, and abdominal pain have manifested as the major symptoms in patients with RMPS [1, 3, 4, 5, 6], while the median age was found to be 35 to 45 years [5]. Among patients with pelvic floor dysfunction, lower gastrointestinal bleeding and RMPS account for 5% and 11% of cases, respectively [11, 12]. Morphologically, lesions of RMP were described as erythematous and edematous (15.4%-47%), ulcerative (32%-33.3%), and polypoid/nodular (21%-51.3%), among which some were covered with fibrinopurulent exudates and, therefore, called "cap polyps" [1, 11]. On endoscopic ultrasound, protruding lesions were found with thickening of the mucosa, ulcerative lesions were observed with thickening of both mucosa and submucosa, whereas relatively flat lesions presented with thickening of the muscularis propria, all of which were associated with no abnormality of the serosal layers [1]. It is worth noting that patients with RMPS were found to have thickened internal anal sphincters, which might be responsible for intra-rectum hypertension and



▶ **Fig. 1** Morphologic phenotypes of rectal mucosal prolapse syndrome under routine colonoscope.

▶ **Table 4** Clinical and endoscopic features of patients diagnosed with RMPS with different morphologic phenotypes.

	Type I	Type II	Type III	Type IV	Type V	P value
Ratio	7 (19.4%)	15 (41.7%)	4 (11.1%)	4 (11.1%)	6 (16.7%)	
Age (years)	40.3	40.3	30.5	37.5	37.2	0.899
Gender (M%)	42.9	53.3	100	100	100	**0.037**
Constipation (%)	0	13.3	0	0	0	1
Blood stool (%)	71.4	73.3	75	75	33.3	0.538
Mucus stool (%)	28.6	46.7	75	25	0	0.118
Pain during defecation (%)	42.9	0	0	50	0	**0.007**
Size (cm)		2.47	1.5	0.67	2.75	0.165
Distance (cm)	11.6	8.2	4.5	5	6.8	**0.019**
Ratio of lesion to rectal circumference (%)	100	20	42	25	17	**0.003**

Illustrations: Type I, lesions with circumferential stenosis; Type II, lesions with protrusions; Type III, lesions with both ulcers and protrusions; Type IV, lesions with ulcers; Type V, lesions with flat manifestations.

chronic hypotension [13]. The distance between RMPS lesions and the anal verge was typically 6 to 8 cm and almost never more than 15 cm [1, 14]. Accordingly, in our study, the maximum distance from RMPS lesions to the anal verge was 15 cm, while the mean value was 8 cm. Furthermore, solitary rectal ulcers were predominantly observed on the anterior or anterolateral wall of the rectum, especially over the rectal folds [6, 10, 15]. Histologically, hyperplastic and disrupted glands, fibromuscular obliteration in lamina propria, and splaying and thickening of muscularis mucosa, had been widely observed in lesions of RMPS, especially SRUS [4, 16, 17]. In addition, submucosal cysts or lakes of mucus can be present in localized colitis cystica profunda [18]. Interestingly, although not involved in our study, IBD, especially ulcerative colitis (UC), may be easily confused with RMPS, particularly in patients who have a history of UC. In such cases, fibromuscular obliteration, and "diamond shaped crypts" are essential for making an eventual diagnosis [4]. As a benign disorder, RMPS also has been reported to be associated with MRT. Patients initially diagnosed with RMPS may develop malignancy later, especially if they have loss expression of the gene *hMLH1*[19, 20]; therefore, histological examination must be performed with caution.

Our study innovatively explored possible factors to help distinguish RMPS and MRT before histologic examination. To our knowledge, this is the first retrospective study rather than merely clinical experience to confirm that, compared with lesions from MRT, RMPS is smaller and more commonly observed in patients who are younger and have a longer disease course.

Furthermore, we have surprisingly found that females are prone to lesions that protrude. In patients with ulcers, they seem to involve a smaller proportion of the rectal circumference, according to our data. Compared with only protrusions, lesions with only ulcers were found closer to the anus. Undoubtedly, there are still some limitations of our study, which could be further improved for more convincing conclusions. First, data on patients in our study were retrospectively collected, and thus, some of clinical information, especially chief complaints and blood test results, were lacking. Second, even though we combined data from Union Hospital, Tongji Medical College, the number of patients eventually diagnosed as RMPS in our study still seems too small to draw more accurate conclusions. Last but not least, only routine colonoscopy was conducted in the study, and few patients were willing to return to the hospital for further colonoscopic examinations of RMPS.

Conclusions

In conclusion, our study suggests that patient age, disease course, and lesion size may help differentiate between RMPS and MRT. We have described five phenotypes according to findings on routine colonoscopy and features of ulcers/protrusions. A multicenter, prospective, and systematic study is warranted for better management of RMPS in the future.

Data availability statement

The data presented in our research are available on request from the authors.

Conflict of Interest

The authors declare that they have no conflict of interest.

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