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Endoscopic Mucosal Resection is Superior to Rectal Suction Biopsy for Analysis of Enteric Ganglia in Constipation and Dysmotility

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Abstract

Background and Aims—Patients with chronic constipation or motility disorders may be referred for rectal suction biopsy (RSB) to rule out Hirschsprung's disease (HD). RSB may not be successful beyond infancy due to the increased thickness of rectal mucosa. Endoscopic mucosal resection (EMR) could improve the diagnostic yield for HD when compared with traditional RSB because of the larger and deeper samples acquired for analysis.

Methods—In this prospective, single-center study, patients referred for RSB were offered enrollment for concurrent EMR. Specimens were analyzed pathologically for size, submucosal ganglionic tissue, and acetylcholinesterase or calretinin staining. Biopsy results were compared with transit studies, anorectal manometry, and constipation severity through validated questionnaires.

Results—Seventeen patients (2 male, 15 female, mean age 35.8 years, range 22–61 years) were enrolled in the study from 2008–2014. All subjects underwent anorectal manometry (88% with anorectal dysfunction, 68% with outlet obstruction) and transit studies (41% with delayed transit). There were no reports of complications from the RSB and EMR procedures. The RSB sample volumes were significantly lower than EMR samples (0.023 cm^3 vs. 0.26 cm^3, p=0.001). There was diagnostic tissue for submucosal visualization by RSB in 53% (9/17) of cases compared to 100% (17/17) with EMR (p=0.003). No cases of HD were diagnosed by RSB; one patient had rare ganglions observed by EMR.

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Conclusions—EMR provides greater tissue volumes and can improve the characterization of ganglion cells in rectal tissue compared to RSB in patients with moderate to severe constipation with suspected HD.

INTRODUCTION

Hirschsprung's disease (HD) or aganglionosis occurs in one in 5,000 births and is considered a rare disorder.[1] Although patients with HD usually present in the newborn period, a subset of patients present later in life with severe chronic constipation, a very common complaint in gastroenterology and primary care practices. Many adult and pediatric patients with chronic constipation ultimately require a biopsy to rule out the presence of aganglionosis as the underlying etiology.

The traditional approach to obtaining rectal tissue has been the rectal suction biopsy (RSB) since the technique was first described in 1969.[2] While RSB has been shown to be safe and effective, limitations are well described. RSB is less likely to provide adequate submucosa for identification of ganglion cells after 3 years of age, with RSB performed in patients 10 years or older only having a reported diagnostic yield of 49% due to the increased thickness of the rectal mucosa beyond infancy.[3] Inadequacy of the specimen is a concern even in clinical trials involving infants, with the reported incidence of inadequacy varying from 10% to more than 30%.[2,4–7] Disadvantages include the blind approach, requirement for two operators, poor suction control, and inconsistency in the size and depth of the specimen.[8] Patients with non-diagnostic specimen in which HD is suspected require surgical full thickness biopsy, involving an invasive surgical procedure, and additional administration of general anesthesia.

Endoscopic mucosal resection (EMR) is an endoscopic technique devised in 1984 as an application of endoscopic snare polypectomy that has been applied to esophageal tissue, gastric tissue, and to rectal tissue for the removal of large colonic polyps.[9,10] Tissue specimens obtained by EMR contain mucosa, muscularis mucosa, and submucosal layers. Incidence of complications associated with EMR in patients with large polyps in the rectum or with large superficial rectal neoplasms vary, however in a large studies of EMR for colorectal neoplasia and polyps have demonstrated a rate of perforation of 0.2–0.35%, intraprocedural bleeding 2–24%[11] and post-procedural bleeding of 1–2%.[3,12] The risk of one small EMR in the rectum has not been studied in large groups of patients, but presumably has a lower risk than that seen with large resections of colonic tumors as in prior studies.

We sought to compare the performance characteristics of the two techniques and assess the relationship between the pathology results and the clinical presentations. EMR of rectal tissue could improve the diagnostic yield for HD when compared with traditional RSB because of the larger and deeper samples acquired for analysis.

PATIENTS AND METHODS

Patient enrollment

In this prospective, single-center study, patients referred for RSB at Massachusetts General Hospital (MGH) between April 2008 and November 2014 were offered concurrent EMR. Inclusion criteria included age greater than or equal to 10 and a clinical indication for RSB to rule out the diagnosis of HD. Exclusion criteria include subjects with coaguloapathy, thrombocytopenia, or any contraindication to general anesthesia, conscious sedation, or endoscopy. Prior to undergoing any procedure, patients had constipation severity assessed through validated questionnaires [Rome III criteria for functional disorders, Irritable Bowel Syndrome Quality of Life (IBS-QOL), Gastrointestinal Symptom Rating Scale (GSRS), and Bristol Stool Scale (BSS)].

Study Procedures

Enrolled subjects had EMR following RSB (Model SBT-100, Medical Measurements Inc, Hackensack, NJ), with the type of sedation (conscious versus general anesthesia) not altered by participation in the study. All procedures were performed on an outpatient basis and patients were not required to undergo full colonic prep; patients underwent fleet enemas prior to the procedure. EMR uses a transparent plastic cap mounted to the tip of a standard endoscope with a snare pre-looped to cut lesions that are suctioned into the cap (Cook Ireland Ltd, Limerick, Ireland). All EMR samples were collected on the posterior rectal wall 2-4 cm above the dentate line and no saline was used to lift the mucosal tissue. The additional rectal tissue obtained by EMR underwent the same pathologic evaluation as the RSB specimens. Specimens were analyzed for volume of sample, presence of submucosal ganglionic tissue, and underwent acetylcholinesterase (cases prior to August 2010) or calretinin staining (cases after August 2010) per MGH pathology protocol. A specimen was diagnostic if there was sufficient submucosal tissue to visualize ganglia and rule out HD (Figure 1). A specimen was deemed non-diagnostic if it was too small to permit tissue analysis, did not contain sufficient submucosal tissue, or contained anal mucosal tissue. Review of clinical data for the study was approved by the Institutional Review Board at MGH on 10/24/2007 with re-approval on 3/8/2017 (Protocol# 2007P001577).

Statistical Analysis

The primary outcome was the proportion of patients with adequate specimen for pathologic examination. Secondary outcome variables included tissue sample volume, fidelity of acetylcholinesterase or calretinin staining, and evidence of abnormal motility on anorectal manometry and colonic transit studies. Differences in proportions were compared using the Fisher’s exact test, differences in means using a two-sided t-test. Linear regression was performed with clinical parameters and results of histopathology using both techniques.

RESULTS

Primary endpoints

Seventeen patients (2 male, 15 female, mean age 35.8 years, range 22-61 years) were enrolled in the study from 2008-2014 (Table 1). Of the seventeen patients offered EMR

following RSB, all seventeen accepted participation. The RSB sample volumes were significantly lower than EMR samples (0.023 cm^3 vs. 0.26 cm^3, p=0.001). RSB was diagnostic in 53% (9/17) of samples, with 47% (8/17) of cases non-diagnostic to exclude HD (Figures 2, 3). All samples (100%, 17/17) collected by EMR were diagnostic, which reached statistical significance with respect to data fidelity compared to RSB (53% vs 100%, p=0.003) (Figure 4). There were no reports of bleeding, perforations, or complications from the RSB and EMR procedures. No cases of HD were diagnosed by either procedure; one patient had rare ganglions observed by EMR. All EMR biopsies were performed 2-4 cm from the dentate line on the posterior wall of the rectum.

Secondary endpoints

In samples where sufficient tissue was obtained, Acetylcholinesterase staining was diagnostic in 75% of cases (3/4), Calretinin staining was Diagnostic for interpretation in 100% (13/13). By Rome III criteria, 10 subjects had IBS-C, 6 subjects had Functional Constipation, and all had at least moderate symptom severity by IBS-QOL and GSRS. All subjects underwent anorectal manometry (88% with anorectal dysfunction, 68% with outlet obstruction) and transit studies (41% with delayed transit). There was no correlation between symptom severity, presence of ganglion cells on histology, acetylcholesterase or calretinin staining, or manometry findings.

DISCUSSION

In this prospective, single-center study, patients with severe constipation with clinical indication to undergo rectal suction biopsy (RSB) to rule out Hirschprung's disease (HD) were offered concurrent endoscopic mucosal resection (EMR). EMR is an endoscopic technique generally used in the removal of large colonic polyps and prior to this study has not previously been studied as an alternative to RSB for obtaining submucosal rectal tissue to exclude the diagnosis of HD. There was significantly more rectal tissue collected per biopsy when using EMR versus RSB. Our primary endpoint, the proportion of patients with adequate specimen for pathologic examination, reached statistical significance as only 53% of samples collected by RSB were adequate for analysis compared to 100% collected by EMR. Neither technique had any reported complications including significant bleeding or perforation.

EMR differs from RSB in that it is not a blind approach, does not require two operators, and has not previously demonstrated inconsistency in the size and depth of the specimen obtained. Each patient in the study underwent both procedures, and because all samples collected by EMR were diagnostic thus excluding HD, no patients had a clinical indication to undergo surgery for a full thickness rectal biopsy. There were no cases of HD were diagnosed by either procedure, however one patient was noted to have rare ganglions by EMR with the corresponding RSB sample non-diagnostic for analysis. A cost analysis was not performed, however at the tertiary center of study, EMR is a more readily available tool than RSB in the adult patient population.

There were several limitations in this study. This was a relatively small study of 17 patients that while underpowered to determine a difference in clinical outcomes (i.e. incidence of HD

diagnosed by each method) was sufficiently powered for the primary endpoint of the diagnostic utility of pathology samples collected by EMR versus RSB. Despite this sample size, our reported diagnostic yield of 53% for RSB samples was consistent with the previously reported 49% in a larger study of this patient population.[3] While constipation severity was assessed through use of validated questionnaires, this study did not assess for differences in patients' perspective regarding the two techniques. Additionally, the location of EMR for this study was limited to the posterior wall of the rectum 2-4 cm above the dentate line. EMR has been previously demonstrated to have a low risk profile in the context of removing large colonic neoplasia[11], however using EMR in healthy colonic rather than rectal tissue would theoretically pose a higher risk than the 0% complication rate in this study as colonic tissue is more likely to perforate than rectal tissue. Future study that addresses these limitations is warranted given this early evidence of the potential diagnostic utility in utilizing EMR to diagnose HD over the standard method of RSB.

Although the 0% complication rate should be taken in the context of a relatively small sample size of 17, EMR was specifically performed in the rectum before the peritoneal rectal shelf and therefore underneath the peritoneal reflection for safety reasons to help prevent any complications such as perforation. To further the safety profile of this application of EMR, endoscopic ultrasound (EUS) could theoretically be used to approximate rectal thickness in the proposed area of biopsy, however as EMR samples are largely limited to submucosal tissue this was not attempted in this study. Additionally, while saline lifting is commonly used to perform EMR in non-rectal tissue, it was not performed in this study and may theoretically decrease the diagnostic yield of obtaining sufficient neuronal tissue for diagnosis by limiting the tissue layers that could be obtained. Targeting the posterior wall of the rectum 2-4 cm above the dentate line has the advantage of safety due to the thickness of the rectal layer at that site and there were no reported adverse events such functional or mechanical changes following the procedure.

In prior study, RSB performed in patients 10 years or older has only a reported diagnostic yield of 49% due to the increased thickness of the rectal mucosa beyond infancy.[3] In the adult population of patients with chronic constipation, the authors would propose EMR as the procedure of choice in patients with refractory constipation that are not responsive to medical therapy if there is clinical suspicion for HD. This patient population typically first undergoes anorectal manometry. Demonstration of an abnormal (i.e. absent) rectoanal inhibitory reflex (RAIR) is classically associated with HD, however a significant portion of this subpopulation has pelvic dysynergia rather than HD from a dilated rectum. Additionally, a prior study has demonstrated that RAIR was absent in only 64% of patients with HD, frequently casting doubt on the diagnosis of HD.[13] Therefore, in patients 10 years or older with chronic constipation refractory to medical therapy and biofeedback, it is reasonable to perform EMR for the exclusion of HD given the relatively low risk of the procedure however additional study that is sufficiently powered to examine clinical outcomes may be warranted to determine if EMR should be standard of care for the diagnosis of HD.

This study demonstrated a potential new application of an existing technique, EMR. Among adult patients with severe constipation in which there is clinical suspicion for HD as a potential etiology, the method of RSB has a relatively low diagnostic yield of approximately

50%. Given the advancements in endoscopic technique that have occurred since RSB was first described in 1969, this study has served as a proof of concept that an existing technique that is widely available at tertiary care centers may serve as an alternative method of diagnosing HD in the adult population. While EMR has been established as a therapeutic and diagnostic procedure for removal of superficial carcinomas or premalignant lesions, this is the first systematic case series evaluating EMR against the traditional technique of RSB, and demonstrated a significant improvement in diagnostic yield with EMR. The clinical utility of improving diagnostic accuracy through a relatively safe outpatient procedure that does not require colonic prep thus preventing an invasive, additional procedure such as surgical full thickness rectal biopsy has immediate clinical implications.

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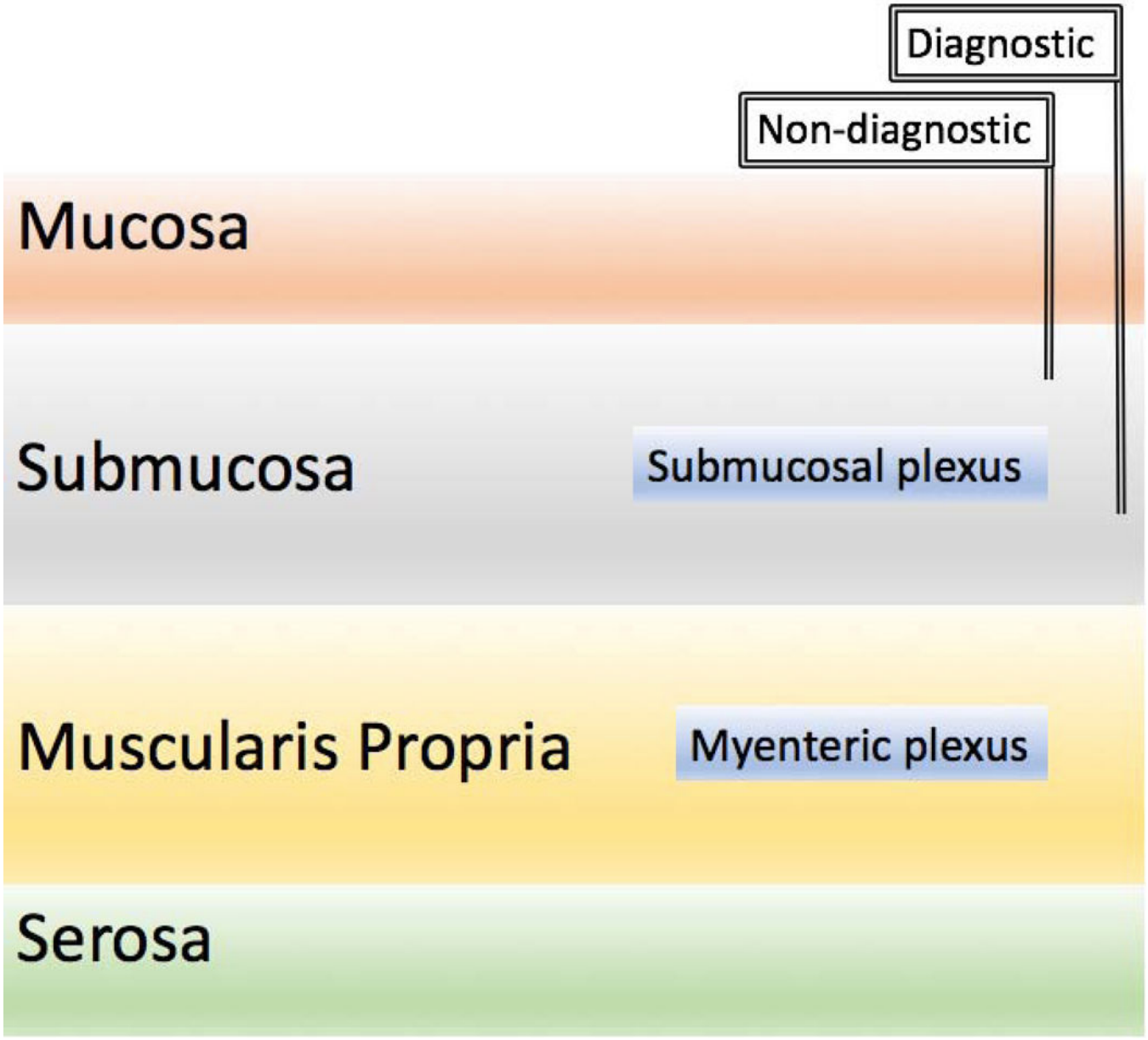

Figure 1.
Diagram demonstrating diagnostic versus non-diagnostic rectal sample for diagnosis of Hirschsprung's Disease

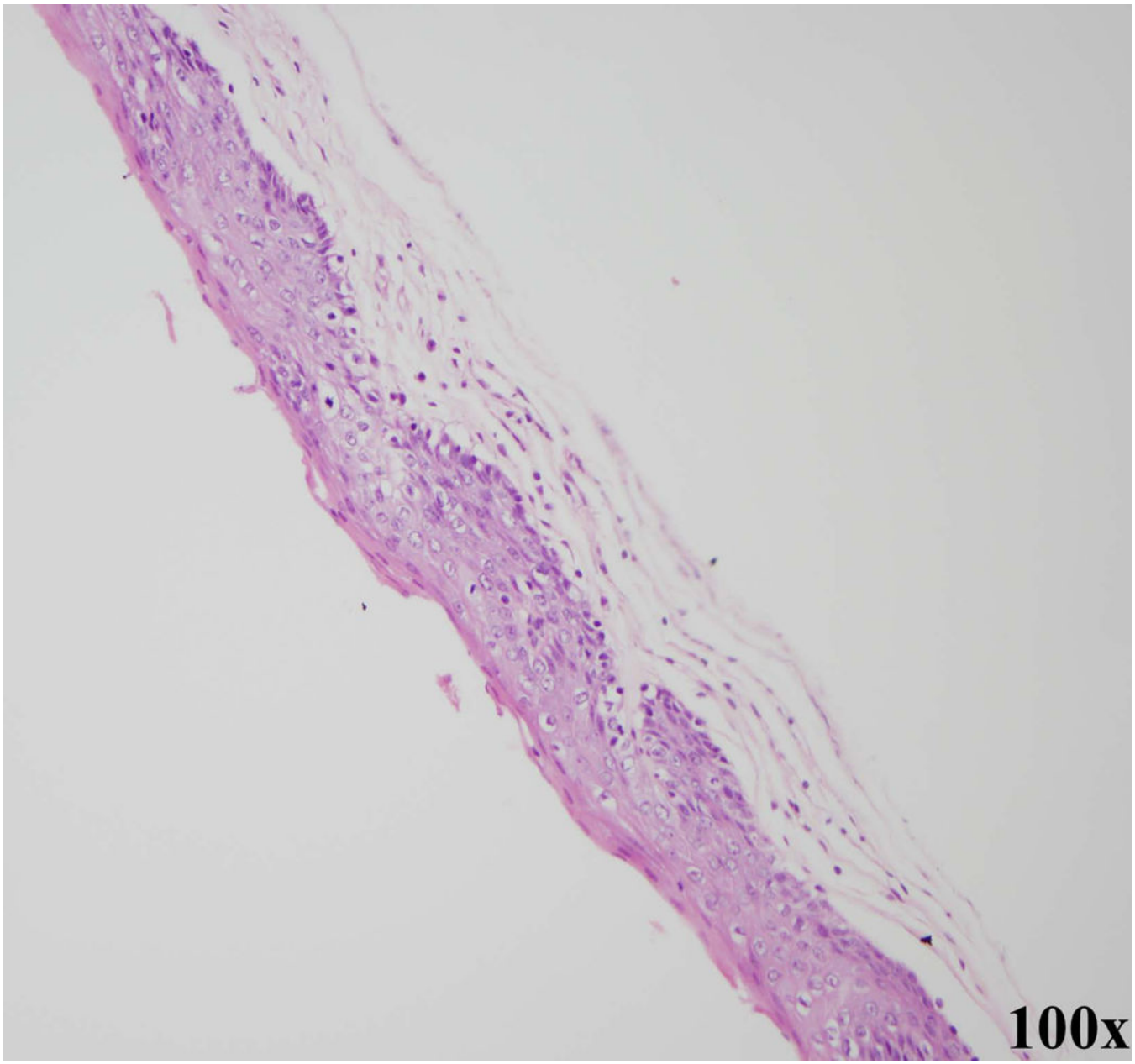

Figure 2.
Non-diagnostic sample collected by rectal suction biopsy (RSB)

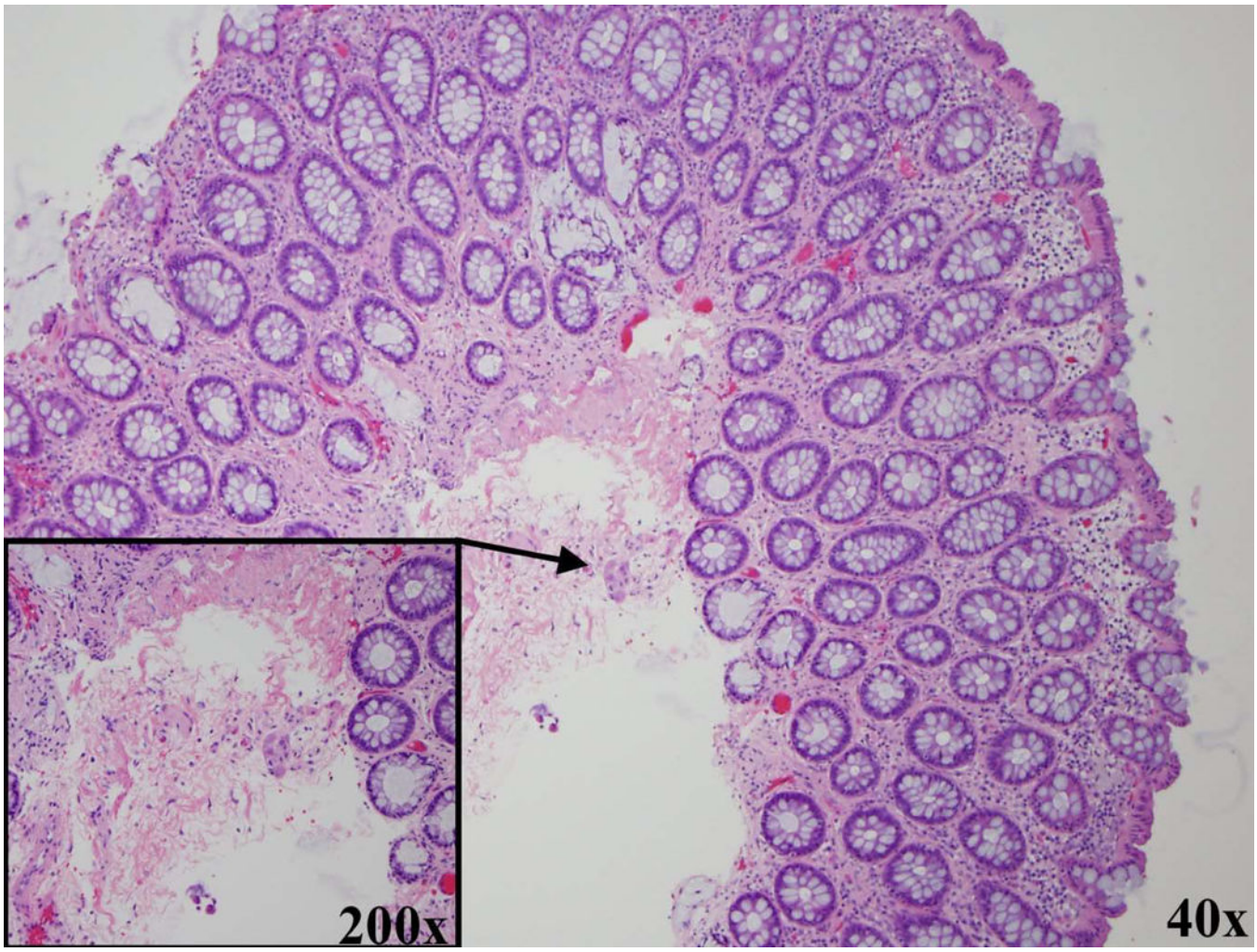

Figure 3.
Diagnostic sample collected by rectal suction biopsy (RSB) showing limited submucosa, inlet image of a submucosal ganglion

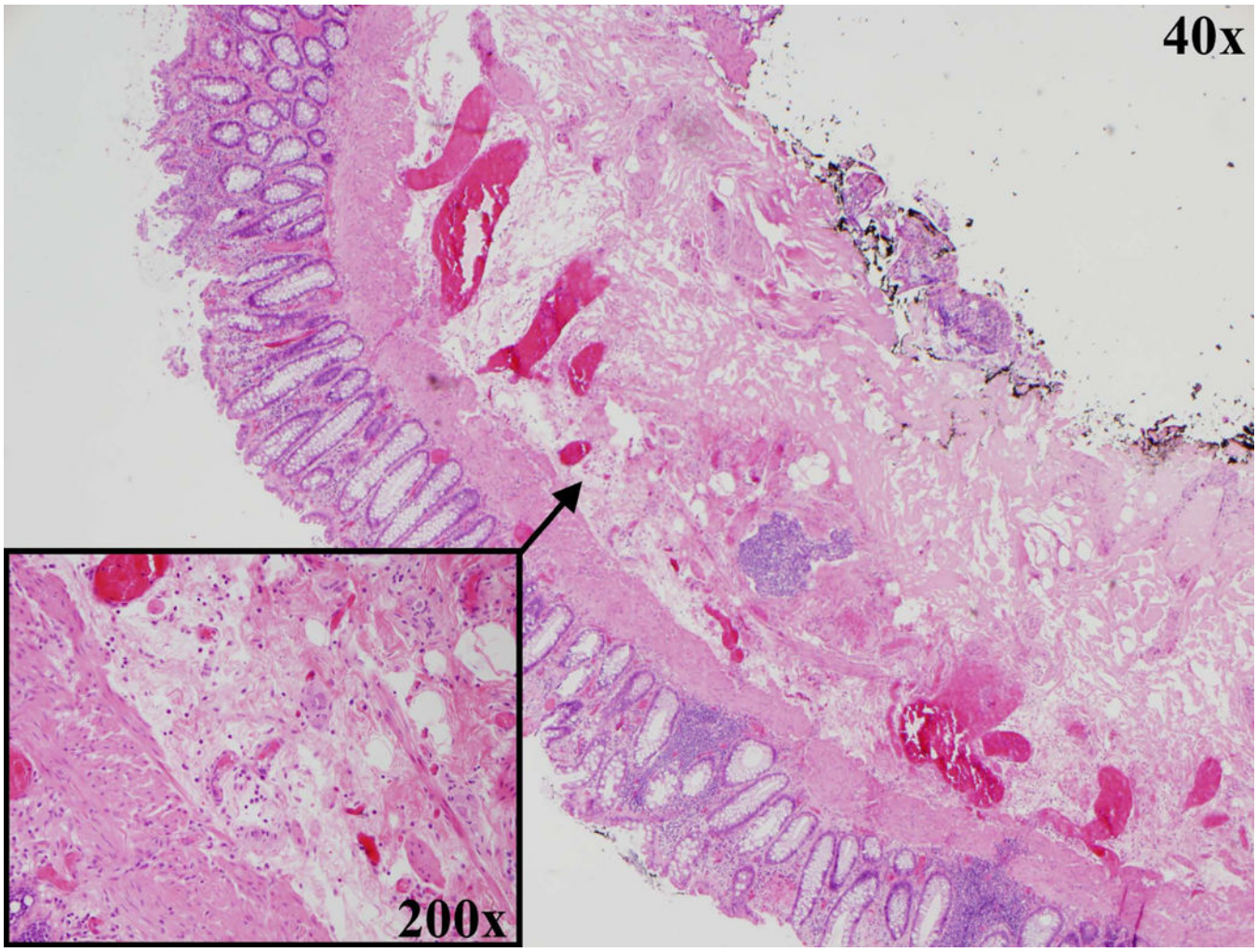

Figure 4.
Diagnostic sample collected by endoscopic mucosal resection showing abundant submucosa, inlet image of a submucosal ganglion

Table 1

Subject demographics and respective diagnostic utility (ND = non-diagnostic) of rectal suction biopsy versus endoscopic mucosal resection.

			Rectal Suction Biopsy (RSB)		Endoscopic Mucosal Resection (EMR)	
Subject	**Age at Biopsy**	**Gender**	**Pathology Result**	**Sample Volume (cm^3)**	**Pathology Result**	**Sample Volume (cm^3)**
1	38	Male	Diagnostic	0.016	Diagnostic	0.810
2	44	Female	ND	0.048	Diagnostic	0.144
3	43	Female	ND	0.008	Diagnostic	0.160
4	44	Female	ND	0.002	Diagnostic	0.126
5	32	Female	Diagnostic	0.008	Diagnostic	0.42
6	29	Female	Diagnostic	0.002	Diagnostic	0.550
7	23	Female	Diagnostic	0.180	Diagnostic	0.216
8	57	Male	Diagnostic	0.032	Diagnostic	0.042
9	22	Female	Diagnostic	0.027	Diagnostic	0.168
10	17	Female	Diagnostic	0.018	Diagnostic	0.096
11	31	Female	ND	0.012	Diagnostic	0.009
12	61	Female	Diagnostic	0.027	Diagnostic	0.750
13	25	Female	ND	0.001	Diagnostic	0.112
14	31	Female	ND	0.001	Diagnostic	0.240
15	59	Female	ND	0.002	Diagnostic	0.242
16	52	Female	ND	0.004	Diagnostic	0.160
17	22	Female	ND	0.002	Diagnostic	0.120