Clip Artifact after Closure of Large Colorectal Endoscopic Mucosal Resection Sites:
Incidence and Recognition

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Abstract

Background: Clip closure of large colorectal endoscopic mucosal resection (EMR) defects sometimes results in bumpy scars that are normal on biopsy. We refer to these as "clip artifact." If unrecognized clip artifact can be mistaken for residual polyp, leading to thermal treatment and potential adverse events.

Objective: To describe the incidence of and define predictors of clip artifact.

Design: Review of photographs of scars from consecutive clipped EMR defects.

Setting: University outpatient endoscopy center.

Patients: 284 consecutive patients with clip closure of defects after EMR of lesions $\geq$ 20 mm and follow-up colonoscopy.

Interventions: EMR, clip closure

Main outcome measurements: Incidence of clip artifact

Results: 303 large polyps met the inclusion criteria. On photograph review, 96 scars (31.7%) had clip artifact. Clip artifact was associated with increased numbers of clips placed (OR for each additional clip 1.2; 95% CI, 1.02 - 1.38) but not polyp histology, size or location. The rate of residual polyp by histology was 8.9 % (27/303), with 21 of 27 scars with residual polyp evident endoscopically. The rate of residual polyp evident only by histology in scars with clip artifact (3/93; 3.2%) was not different from the rate in scars without clip artifact (3/189;1.6%).

Limitations: Retrospective design. Sites closed primarily with one type of clip. Single operator assessment of endoscopic photographs.

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Conclusions: Clip artifact occurred in the scars of about a third of large clipped EMR sites and increased with number of clips placed. Clip artifact could be consistently distinguished from residual polyp by its endoscopic appearance.

Introduction

In 2006, we began to systematically close large endoscopic mucosal resection (EMR) defects in the colorectum with hemostatic clips [1]. We previously reported that clipping substantially reduced the incidence of delayed hemorrhage relative to historical controls [1].

At follow-up colonoscopy to inspect colorectal EMR scars, the scars are typically flat and smooth in the absence of residual polyp and when no clips were placed to close the EMR defect. At follow-up colonoscopy to inspect the EMR scar for residual polyp we observed that after clipping some scars had bumps of tissue on or adjacent to the scar. These bumps or distortions of the scars had normal pit patterns and on biopsy demonstrated normal tissue. We refer to these distortions in the scar as "clip artifact." If not recognized as normal tissue, clip artifact can be mistaken for residual polyp, which could lead to the unnecessary application of thermal injury using snare polypectomy or ablative therapy. In this report we describe the incidence of clip artifact and the successful differentiation of clip artifact from residual polyp.

Methods

We performed a retrospective assessment for the appearance of "clip artifact" in a database of large colorectal lesions maintained for quality control purposes. The database contains relevant information on all large (≥20 mm) non-pedunculated lesions resected by DKR since January 2000. This information is prospectively and periodically updated [1]. Permission to review the deidentified database was obtained from the Institutional Review Board at Indiana University

Health with exempt status. To be included in the current study the EMR defect had to be clipped, the first follow-up colonoscopy had to be performed at one of our endoscopy units, and high quality photographs of the site at first follow-up had to be available for review.

The original EMR and the follow-up colonoscopies were performed by a single endoscopist (DKR) or by a gastroenterology fellow under his direct supervision. All procedures involving clipping and the follow-up examinations were performed using Olympus (Olympus America Corp; Center Valley PA) colonoscopes of the 180 or 190 series. The clips placed were largely Resolution (Boston Scientific Corp, Natick, MA) but for some recent cases the Instinct (Cook Medical, Inc.) or a combination of clips were used. The first follow-up procedure was performed 4 to 6 months after the original EMR in almost all cases. At the follow-up procedure the site was inspected in white light and narrow band imaging. Clean scars and clip artifact were differentiated from residual polyp by their normal pit patterns. If the scar showed either no clip artifact and no residual polyp or some area of clip artifact and no residual polyp then cold biopsy forceps were used to take biopsies of the site. Samples were taken in all cases from both the clip artifact and the flat scar and placed in the same bottle for histologic analysis. The approach to biopsies of the scar was to take cold samples at closely spaced intervals from the full length of the scar. Most samples were from the scar and not from normal-appearing mucosa adjacent to the scar. If residual polyp was evident it was resected using snare polypectomy with electrocautery and the tissue specimen was placed in a separate bottle from cold biopsy specimens of the remaining flat scar and any clip artifact that was also present. The rim of the thermal injury from snaring was then treated with argon plasma coagulation (APC) in an effort to reduce the chance of residual polyp at subsequent follow-up.

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The database includes information on polyp size, location, number of clips placed after the EMR and the results of histology from the original EMR and all tissue collected at follow-up procedures. Included polyps were divided into right colon (cecum, ileocecal valve, ascending), transverse colon (hepatic flexure, transverse and splenic flexure) and left colon (descending, sigmoid and rectum). In this report the histologies are referred to as conventional adenomas or serrated lesions (sessile serrated polyps and hyperplastic polyps). Photographs of the scars at follow-up were reviewed by DKR to determine the presence of clip artifact or residual polyp based on the appearance of the scar. During the photograph review DKR was blinded to the procedure report of the colonoscopy performed to inspect the EMR site. Clip artifact when present was classified grade I, grade II, grade III, or grade IV based on the presence of number of discrete bumps- 1, 2, 3, and $\geq$ 4 bumps, respectively. As a check on the accuracy of the photographic review, we also reviewed all procedure reports to make certain that the actions taken by DKR at the follow-up procedure were consistent with the photographic review, i.e. sites interpreted as residual polyp had been treated at follow-up using snare polypectomy and APC and sites interpreted as clip artifact were subjected to cold biopsy only. In all cases the photograph interpretation and the actions at the follow-up procedure were consistent.

Statistical analysis

We report descriptive characteristics of polyps originally resected along with the number of clips used to close the EMR sites. The Fisher exact test was used to determine the difference in occurrence of recurrent polyp tissue among clip artifact and non-clip artifact groups. The Fisher exact test and ANOVA were used to determine the association of polyp size, location, pathology and number of clips with the grade of clip artifact observed. Using a binary logistic regression

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analysis we examined if any of the above factors predicted the occurrence of clip artifact at follow-up. We used Hosmer-Lemeshow goodness of fit test to assess the model. We report odds ratios (OR) with 95% confidence intervals (CIs). The statistical significance was set at 0.05. All analyses were performed using SAS (version 9.4, SAS Institute Inc.: Cary, NC).

Results

There were 322 EMR sites in 284 patients that were clipped and had first follow-up colonoscopy at our site, of which 19 had no or inadequate photographs of the EMR scar at follow-up. These 19 were excluded from further analysis. Of the 19 excluded polyps, none were treated with thermal therapy at follow-up of the site, all had biopsy specimens taken of the scar, none had histologic evidence of residual polyp. There were 303 EMR sites with high quality photographs, and of these all but 18 had biopsy specimens taken of the scar. Of the 18 EMR sites without scar biopsies, only 1 was considered to have clip artifact on photograph review, which was graded at 1+. Of these 18 polyps without scar biopsy at first follow-up, 17 had a subsequent follow-up (after the first follow-up) at our institution. None of the 17 had visible residual polyp and 11 had biopsies of the scar at the second follow-up and these biopsies were negative for residual polyp in all 11 cases. For the purpose of calculating residual polyp rates we considered all 18 of these EMR sites to be negative for residual polyp.

There were 260 conventional adenomas and 43 serrated lesions. Polyp size ranged from 20 to 100mm with a mean size of 29.9 ±9.7 mm. The details of polyp location are shown in Table 1. The majority of lesions were in the right colon (n = 200; 66%) or transverse (n = 66; 22%) and 37 (11%) were in the left colon. The number of clips used to close the EMR site ranged from 1 to 11 with mean 3.9 ± 1.8.

On review of the photographs, 96 scars (31.7%) were considered to have clip artifact, including three that had both clip artifact and endoscopically evident residual polyp. The degree of clip artifact (I, II, III, and IV) was 53.1% (n=51), 26% (n=25), 11.5% (n=11), 9.4% (n=9), respectively. Figure 1 shows examples of clip artifact by grade.

Among the 96 scars with clip artifact, there were 6 scars with residual polyp identified histologically (4 conventional adenomas and 2 serrated lesions). The 6 scars with residual polyp confirmed by histology included the 3 polyps with endoscopically evident residual polyp (in these cases polyp was identified only in the endoscopically evident polyp and was not found in the biopsies of the normal-appearing scar and clip artifact) and in 3 scars polyp tissue was identified histologically only by biopsies of flat scar plus clip artifact. Figure 2 shows examples of sites with both clip artifact and residual polyp.

There were 92 scars with clip artifact confirmed by biopsies showing no histologically identifiable residual polyp (including biopsies from scar and clip artifact areas of the 3 polyps which also had endoscopically evident residual polyp). One scar with clip artifact did not have scar biopsies.

The mean sizes of the polyps in the clip artifact and the non- clip artifact group was 31.3 ±11.3mm and 29.2 ±8.8 mm, respectively. The mean numbers of clips used in the clip artifact group and the non-clip artifact group were 4.3 ± 2.1and 3.6 ± 1.7 respectively.

On regression analysis, polyp location (p = 0.4), pathology (p = 0.29) and polyp size (p = 0.61) did not predict the presence of any clip artifact (Table 2). A higher number of clips placed did predict any clip artifact (OR 1.2; 95% CI, 1.02 - 1.38 for each additional clip placed). None of these factors was significantly associated with the grade of clip artifact.

The total rate of residual abnormal histology (residual polyp) was 8.9 % (27/303), including 24 conventional adenomas and 3 serrated lesions. Of the 27 EMR scars with histologic evidence of residual polyp, 21 were predicted to have residual polyp based on scar photographs, and review of endoscopy reports indicated these 21 sites were treated with thermal therapy. The rate of detecting polyp tissue by histology only in scars that had clip artifact and no endoscopically visible polyp (3 of 93; 3.2%) was not different from the rate of polyp tissue detected only by histology in scars that had neither clip artifact or endocopically evident residual polyp (3 of 189; 1.6%; p = 0.4).

Discussion

In this study we present the first description of clip artifact in colorectal EMR scars. The incidence of clip artifact was 31.7%, and clip artifact was considerably more common than residual polyp. Thus, colonoscopists who use clipping to close colorectal EMR sites, or who may be performing colonoscopy on patients in whom others have performed EMR with clipping, should be aware of and able to identify clip artifact in EMR scars. Our data show that clip artifact can be reliably differentiated from overt residual polyp by its endoscopic appearance (Figures 1 and 2). This is important because clip artifact consists of normal tissue and does not require treatment with thermal resective or ablative therapies. Treatment of polypoid clip artifact with thermal techniques would subject patients to unnecessary risks. Anecdotally, we have

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observed that gastroenterology fellows uniformly think that clip artifact is residual polyp the first time they are exposed to it.

We [2] and others [3] have reported that biopsy specimens of endoscopically normal-appearing EMR sites will sometimes reveal residual dysplastic or serrated tissue. We previously showed that residual tissue on histology but not evident by endoscopy is associated with a higher risk of an eventual or "late" recurrence of polyp in the EMR site [2]. The rate of "histology-only" evidence for residual polyp at first follow-up was numerically higher in patients in the current study who had clip artifact (3.2%) compared to those sites that were flat (1.6%) but both rates were low and the differences did not reach significance. We continue to obtain biopsy specimens of endoscopically normal EMR sites, but we realize that the availability of high definition optics may make this practice unnecessary even in the very near future. We do recommend that clipped EMR sites be examined at follow-up with a high definition colonoscope to allow reliable differentiation of clip artifact from residual polyp.

Although the mechanism of development of clip artifact is uncertain, it seems likely that the presence of the clip distorts the mucosal contour during the healing process. We sometimes see a residual clip still in place at follow-up, and this clip often has an overgrowth of polypoid granulation tissue around its base (Figure 3). We suspect this mound of granulation tissue develops the ultimate appearance seen as clip artifact after the clip detaches and the inflammation in the granulation tissue subsides.

Limitations of this study include that we reviewed photographs to identify clip artifact. However, our retrospective assessments were consistent in all cases with the actions taken by the endoscopist at the time of examination of the EMR scar (i.e. use of thermal therapy vs only cold biopsy). A second limitation is most of this experience was with Resolution clips. Instinct clips are larger than Resolution clips, and might have a different incidence of clip artifact.

Hemostatic clips can be used during EMR to close a perforation [4], reinforce a muscle injury identified by a target sign [5], or to prevent delayed hemorrhage [1]. No randomized controlled trial of clip closure of large EMR sites has been performed, and the current standard of medical care certainly does not require prophylactic clip closure of EMR sites. It is expensive both in terms of clip cost and physician and facility time to perform clip closure. Controlled trials evaluating the benefits of clip closure of large EMR sites are needed. Anecdotally, some experts have expressed concern that clip closure could bury residual polyp. However, we have not encountered this phenomenon. None of the recurrences in this study which had no visible polyp endoscopically were found by histology to have buried polyp tissue. Further, the occurrence of histologically demonstrated residual polyp in EMR sites with no endoscopically visible polyp was described in detail before the use of clip closure [2].

Our current practice is to perform an initial follow-up of large EMR sites 4 to 6 months after EMR. In almost all cases we perform the second follow-up 1 year after the first follow-up. Most endoscopically visible recurrences are small and easily resected at the first follow-up. Waiting a year before the second follow-up provides ample time for any recurrence to develop into a discrete, endoscopically visible lesion that can be subjected to directed endoscopic retreatment.

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Similarly, if the first follow-up shows no endoscopically visible polyp but there is a histologic recurrence, we still wait a year for the second follow-up. Some of these patients never have a visible recurrence [2], presumably because the cold biopsy specimens taken at the first follow-up removed all the polyp tissue. Waiting a year provides an ample interval for any residual tissue to develop into an endoscopically visible discrete lesion that can be treated. Knabe et al. emphasized that there is value in taking biopsy specimens from the EMR site even at the second follow-up when the site appears endoscopically normal [3]. We make an exception to the timing of follow-ups if the first follow-up shows a visible recurrence that is either large or has high-grade dysplasia (both are rare). If a recurrence is large or has high grade dysplasia then we perform the second follow-up 4-6 months after the first. For cases in which both the first and second follow-up show no recurrent polyp by endoscopy or histology, we perform the next colonoscopy in 3 years, unless otherwise indicated by a polyp syndrome or inherited cancer syndrome.

In conclusion, clip artifact is common in EMR scars after clip closure of EMR sites. Clip artifact can be reliably differentiated from residual polyp by its endoscopic appearance. This finding is important, because failure to recognize clip artifact could result in unnecessary and potentially dangerous thermal treatment of EMR scars that are already cured of the original pre-cancerous tissue. We recommend including biopsy samples from clip artifact with biopsy specimens from normal-appearing flat scar when follow-up examination of EMR sites is performed.

Table 1: Location of 303 lesions included in this study

Location	Number (%)
Ileocecal valve	17 (5.6)
Cecum	72 (23.8)
Ascending colon	111 (36.6)
Hepatic flexure	12 (4)
Transverse colon	53 (17.5)
Splenic flexure	1 (0.3)
Descending colon	10 (3.3)
Sigmoid colon	14 (4.6)
Rectum	13 (4.3)

Table 2: Association of location, pathology, polyp size, and number of clips used with the presence of any clip artifact

Risk factor	OR (95% CI) *	p-value
Location		
Right colon	1.37 (0.6-3.16)	0.45
Transverse colon	1.89 (0.75-4.8)	0.18
Left colon	1	-
Pathology		
Adenoma	1.52 (0.7-3.29)	0.29
Serrated	1	-
Size of the polyp	1.01 (0.98-1.04)	0.61
Number of clips used	1.19 (1.02-1.38)	0.03

*Odds ratio for each additional clip placed

Figure legends:

Figure 1. Photographs of endoscopic mucosal resection snare with clip artifact a,b: grade I clip artifact c,d: grade II clip artifact e,f: grade III clip artifact g,h: grade IV clip artifact. In all photographs, arrows designate clip artifact.

Figure 2. a/b: Photographs of endoscopic mucosal resection sites demonstrating both clip artifact (thin arrows) and residual conventional adenoma (thick arrows)

Figure 3. Retained clip on an endoscopic mucosal resection scar. The thin arrows designate 2 areas of established clip artifact. Arrowheads designate polypoid granulation tissue at the base of the retained clip. This tissue may be the precursor that becomes clip artifact after clip detachment.

References:

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Acronyms:

APC: Argon plasma coagulation

CI: Confidence interval
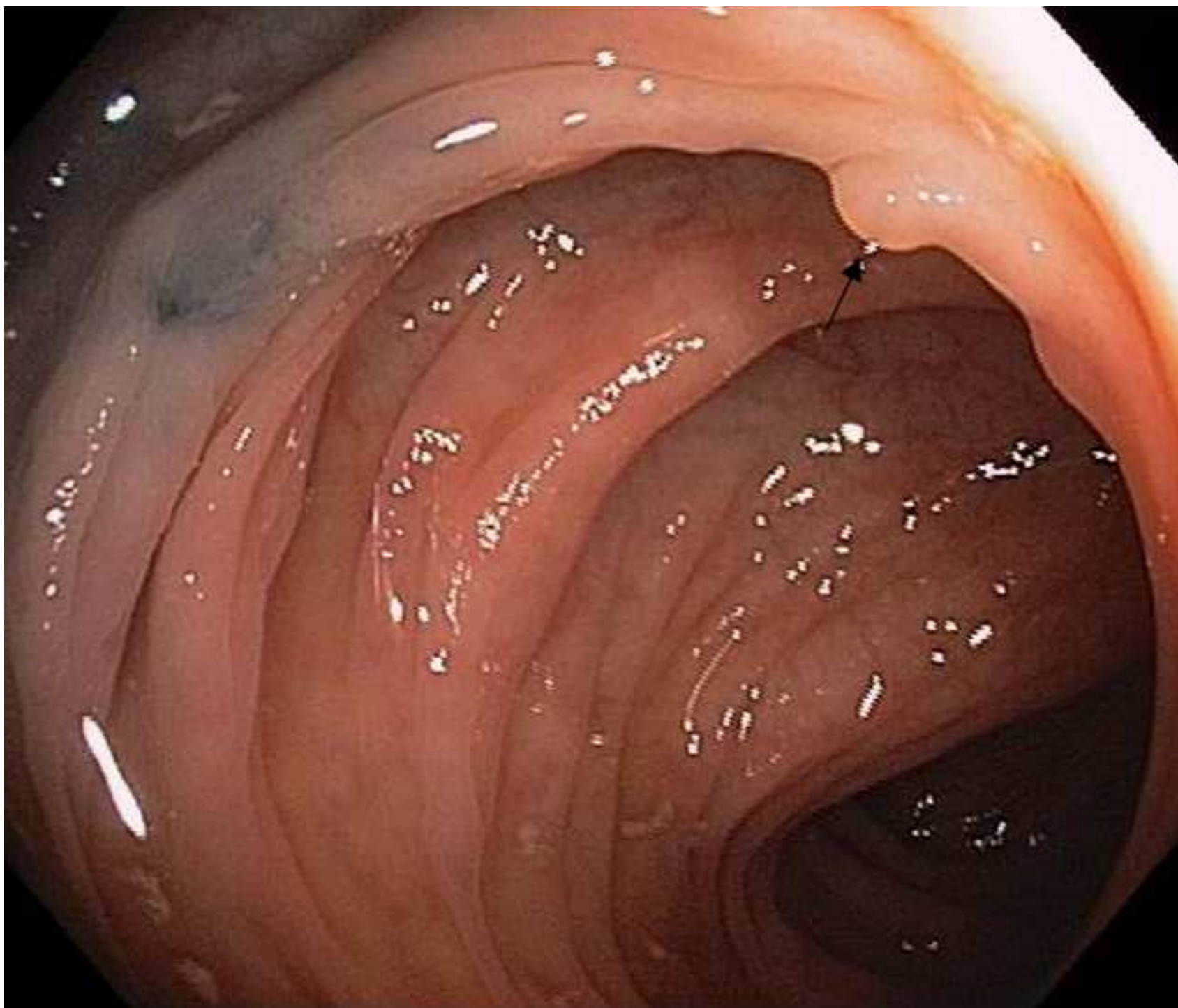
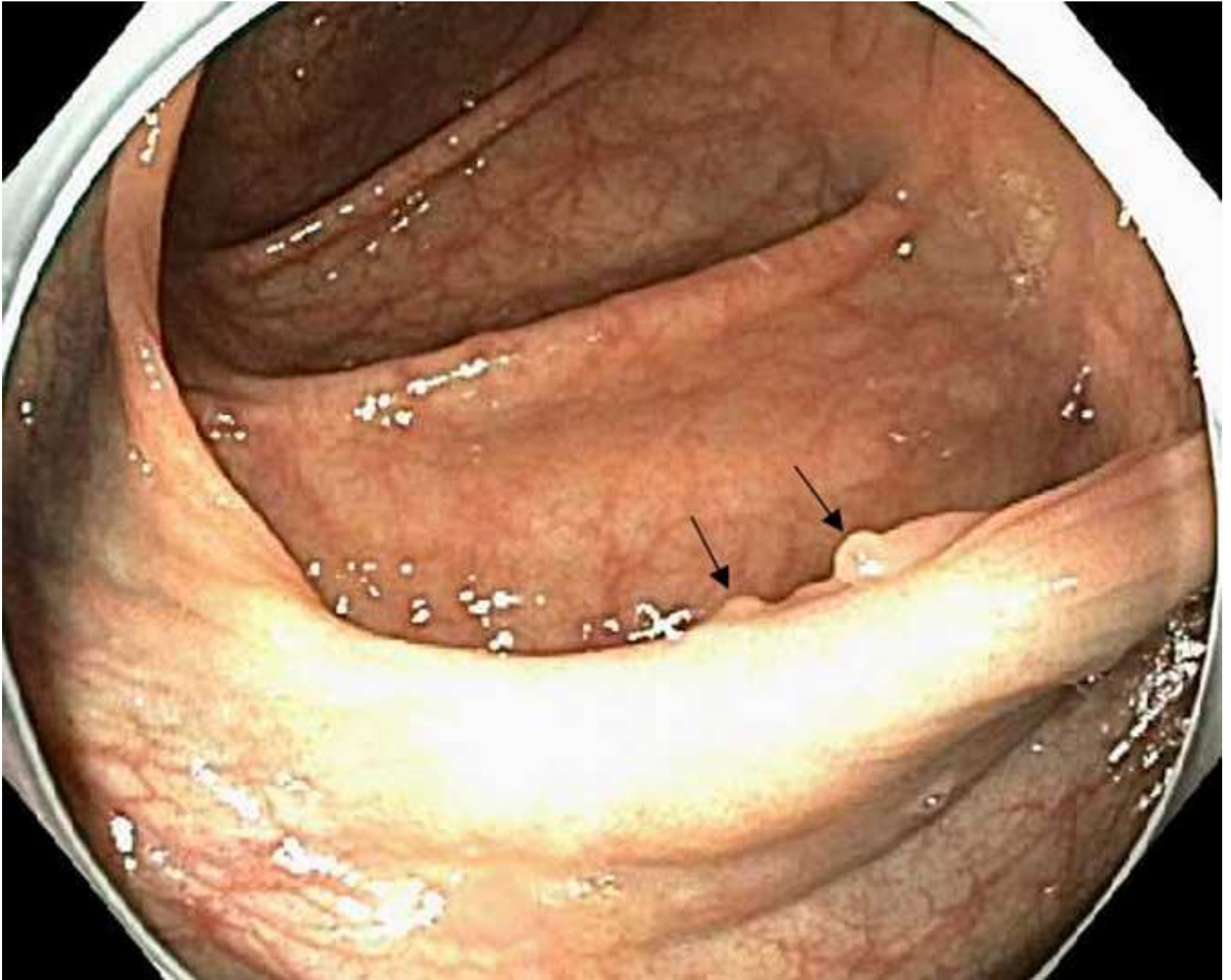EMR: Endoscopic mucosal resection
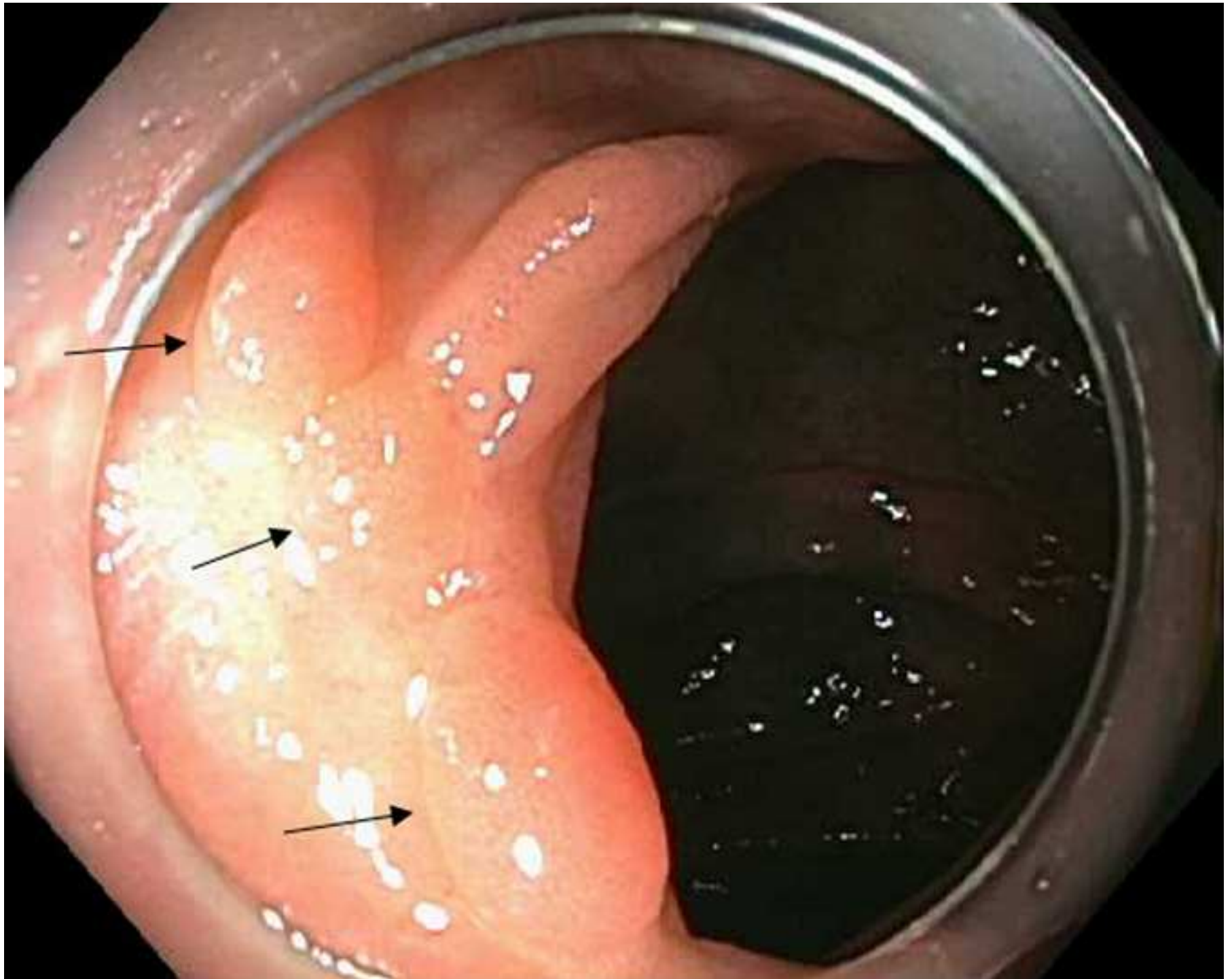
OR: Odds Ratio

Figure(1A)

Figure(1E)

Figure(1F)

Figure(3)