

Potential clinical complications of Orise™ gel use, a new submucosal lifting agent: experience from a tertiary care center and review of the literature

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Abstract

Background Endoscopic mucosal resection (EMR) involves forming a fluid cushion in the submucosal area with a lifting agent, followed by superficial resection. Orise™ gel is one of the commonly used lifting agents for EMR. We present a case series and literature review that analyzes the characteristic histopathological findings and clinical implications observed where Orise™ gel was used before EMR.

Methods Colon resection specimens and prior EMR specimens where Orise™ gel was used were reviewed for patients undergoing EMR between January 2018 and December 2020. The literature review included relevant studies from the Medline and Cochrane databases from January 2018 to December 2020.

Results A total of 12 colon polyp EMRs using Orise gel were performed during the study period. Seven patients (58.34%) underwent surgical resection. Histological examination revealed that, after the EMR procedure, the Orise™ gel material changed its morphological characteristics over time from a basophilic (bluish) non-inflamed pattern to an eosinophilic (pink) type pattern, eliciting a foreign body reaction. The endoscopic appearance and examination of the excised specimens weeks after injection gave the impression of a mass in some cases. The material was also present transmurally and in some cases in the peri-intestinal adipose tissue.

Conclusions It was observed that Orise™ gel use elicits a foreign body-type granulomatous reaction. This potential side effect may lead to overdiagnosis of a mass/lesion and unnecessary surgical interventions. This case series and review of the literature aims to increase awareness of the changes caused by Orise™ gel in the gastrointestinal tract.

Keywords Endoscopic mucosal resection, Orise™ gel, foreign body giant cell reaction, colectomy, colonoscopy

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Introduction

Endoscopic procedures for the resection of mucosal and submucosal lesions include snare polypectomy, endoscopic mucosal resection (EMR), and endoscopic submucosal dissection (ESD). EMR and ESD are minimally invasive methods. Compared to surgical approaches for superficial lesions, they have lower complication rates with a shorter recovery time, provide protection of the gastrointestinal tract's physiological and functional integrity, and are more cost-effective [1]. To prevent deep tissue damage caused by thermal injury during these procedures, a submucosal fluid cushion is created by injecting into the submucosal layer of the colon wall. With the injection, a safe resection area is formed between the muscular layer and the lesion. This method not only reduces the rate of significant complications, such as bleeding and perforation, but can also help determine whether or not the lesion has deep tissue invasion [1].

In the past, normal saline has been used as a lifting agent. However, saline is absorbed rapidly by the submucosal tissue, and repeated injections are needed for the sustained and adequate lifting of the lesion. This has since been replaced by more complex colloidal-viscous solutions, such as dextrose water, hydroxypropyl methylcellulose (HMC), hydroxyethyl starch (HES), hyaluronic acid (HA), succinylated gelatin (SG), fibrinogen mixture, Eleview™ (SIC-8000, Aries Pharmaceutical, La Jolla, Calif), and Orise™ (Boston Scientific, Marlborough, MA, USA). Among these solutions, HES, Eleview™ and Orise™ have been approved by the Food and Drug Administration (FDA). Although Eleview™ and Orise™ have only recently become available, because of their accessibility and the ability to provide excellent submucosal lift they are widely used for EMR procedures [2].

In 2019, our institution started to use Orise™ gel in EMR and ESD procedures for submucosal lifting. Histological examination of the specimens in which Orise™ gel has been used has received little to no attention in the clinical gastrointestinal literature. This article presents the histological findings from the resected colon specimens in 7 unique patients, with the potential clinical implications, and a review of the current literature relating to the use of Orise™ gel as a submucosal lifting agent for polyp resection.

Patients and methods

Orise™ gel was used as a lifting agent at our institution between January 1, 2018, and July 1, 2020. Institutional review board approval was obtained (FLA 21-004). A prefilled, pre-dyed 10 mL syringe kit with a delivery system (23 gauge interject needle catheter) was used for injection in all cases. Patient demographics, details of the endoscopic procedure, including the type of lifting agent, and follow-up surgical intervention/resection, if performed, were extracted from the electronic medical records. Patients with incomplete information and in whom Orise™ gel was not used as a lifting agent were excluded from the study.

Large intestine specimens in which the material characteristics of Orise™ gel were identified, were retrieved and reviewed. The specimens were fixed in buffered formalin, paraffin-embedded, and 4- μ m thick tissue sections were stained with hematoxylin and eosin (H&E). The biopsy tissues of EMR specimens when the Orise™ gel was initially injected (time zero) were also retrieved and examined for this study. The histological appearance of Orise™ in its native state was also obtained by using 20 mL of it wrapped in lens paper, fixed in formalin, paraffin-embedded and placed on H&E-stained slides. In addition, an aliquot was left to dry overnight at room temperature, exposed to air to acquire a more solid consistency.

For the literature search, relevant studies were included by searching the Medline and Cochrane database of clinical trials from January 2018 to December 2020. The database was searched using the following keywords or combinations: endoscopic mucosal resection (EMR), Orise™, injectable lifting agent, colon polyp. The review included all English

language abstracts, manuscripts, and study designs. Two investigators independently reviewed the titles and abstracts for possible inclusion in the study.

Results

A total of 12 patients underwent EMR of colon lesions with Orise™ gel as a lifting agent during the study period (Fig. 1). Of these, 7 patients (58.34%) underwent surgical resection (6: partial colectomy; 1: sigmoidectomy). There were 5 female and 2 male patients between the ages of 52 and 72 years. The demographics and clinicopathological features of the study population are summarized in Table 1. The remaining 5 patients in whom Orise™ gel was used as a lifting agent during colonoscopic EMR with no subsequent surgery, did not demonstrate residual Orise™ gel or typical inflammatory changes on the index histological specimen. Follow-up colonoscopy also did not show any suspicious submucosal mass or nodular findings in these patients.

We analyzed a total of 14 specimens from the 7 patients who underwent surgical resection. The majority of the lesions were identified as Is (Sessile), and lesion size ranged from 12-40 mm. The most common pathological lesion was tubular adenoma, followed by tubulovillous adenoma. Two patients were found to have invasive adenocarcinoma. The indications for surgical resection were as follows: 3 patients had inadequate lifting during EMR; 2 patients were found to have a firm mass with high suspicion of malignancy at the site of a previous EMR during follow-up colonoscopy 6 months later; and 2 patients had well-differentiated adenocarcinoma on the EMR specimen. The interval from the endoscopic injection of Orise™ gel to surgical resection ranged from 13-198 days. All specimens from partial colectomies contained the injected material. The gross and histological examination revealed that the material was not limited to the submucosa. In one of the specimens, Orise™ gel involved the mucosa (*lamina propria*) and *muscularis mucosa*. In 5 of the 7 cases, the *muscularis propria* was also infiltrated by the material. Moreover, in 2 specimens, the material penetrated the *muscularis propria* entirely and extended into the per-intestinal adipose tissue and the serosa (Fig. 2 A, B, patient #3).

Interestingly, in 2 cases, the material created a mass-like effect (Fig. 3 A,B and 4 A,B) visualized on follow-up colonoscopy, but no residual adenocarcinoma or high-grade dysplasia was found on the resected surgical specimen

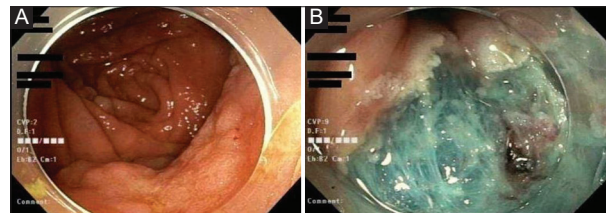


Figure 1 (A) A 40-mm carpeting polyp was found in the cecum. (B) Approximately 18 mL of Orise™ gel was injected submucosally to raise the polyp and create a cushion for the resection. The polyp was successfully resected in a piecemeal fashion using hot snare and hot biopsy forceps

Table 1 Summary of clinical and histological features of patients included in the study

Patient	Age/Sex	Indication/endoscopic appearance and location	Initial histological diagnosis	Procedure and finding	Location of the Orise™ material	Interval from injection to excision (days)	Histological appearance of Orise™
1	70 y/o F	30 mm polypoid lesion central depression (Paris classification IIa+c) Ascending colon	TVA	Partial Right colectomy TVA	Mucosa, submucosa	49	Abundant GCs, small nodules of Orise
2	67 y/o F	30 mm sessile granular lateral spreading lesion (Paris classification Is) Cecum	TVA	Right hemicolectomy TVA	Submucosa, <i>muscularis propria</i>	198	Palisading histiocytes around Orise, many GCs, histiocytes, lymphocytes
3	59 y/o M	40 mm sessile polyp ((Paris classification IIa) Ascending colon	TVA	Right hemicolectomy TVA	Submucosa, <i>muscularis propria</i> , serosa, adipose tissue	13	Infiltrative pattern, paucicellular reaction, bluish mucoid-like, GCs in subserosa
4	52 y/o M	20 mm sessile polyp (Paris classification Is) Sigmoid colon	Invasive carcinoma in a TA	Sigmoid resection No residual carcinoma	Submucosa, <i>muscularis propria</i>	46	Abundant GCs
5*	65 y/o F	40 mm carpet-like sessile polyp (Paris classification Is) Cecum	Invasive carcinoma	Right hemicolectomy No residual carcinoma Re-exploration*	Submucosa, <i>muscularis propria</i> , adipose tissue, serosa	24 36*	Abundant GCs, neovascularization, lymphocytes in fat and subserosa
6	72 y/o F	12 mm lesion (Paris classification IIc) Descending colon	TA with high-grade dysplasia	Transverse descending partial colectomy No residual lesion	Submucosa	93	GCs, small nodules of Orise, fibroblasts
7	59 y/o F	40 mm polyp Ascending colon	TA with high-grade dysplasia	Right hemicolectomy	Submucosa, <i>muscularis propria</i>	140	Abundant GCs, infiltrative pattern.

GC, giant cell; TA, tubular adenoma; TVA, tubulovillous adenoma

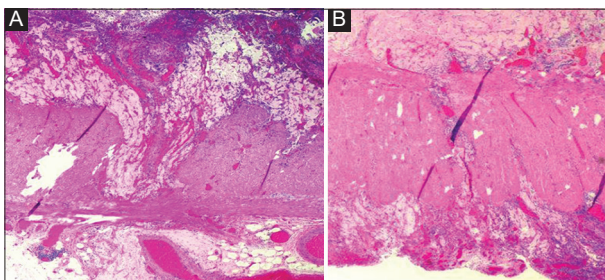


Figure 2 (A) Orise™ gel penetrates the *muscularis propria* into the perintestinal adipose tissue (hematoxylin and eosin, 25×). (B) In other areas, the material reached the serosa causing serositis. (hematoxylin and eosin, 25×)

(patients #4 and #5). One of these patients (patient #5) was found with abundant material and reaction in the adipose tissue on the resected specimen and developed postoperative complications with clinical and imaging evidence of a partial obstruction, 2 weeks after the initial surgical resection. The patient underwent another exploration with further resection

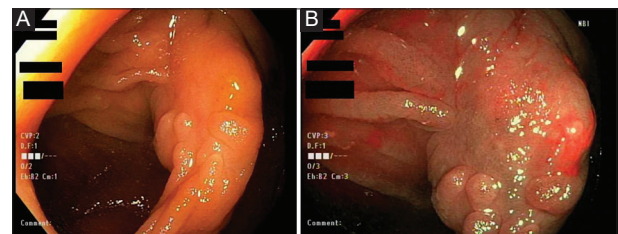


Figure 3 Follow-up colonoscopy demonstrating post-polypectomy scar. (A) High-definition white light endoscopy; (B) narrow band imaging. There does not appear to be any residual mucosal polyp tissue; however, there is a 2-cm submucosal firm nodule suspicious for an underlying mass at the site of previous polyp resection

at the site of anastomosis. Although negative for malignancy, this additional specimen again showed Orise™ gel eliciting the typical giant cell reaction with associated fat necrosis and inflammation by the foreign material.

Histologically, there was variability in the character of the material, depending on the interval between the injection and the examination of the specimen. For instance, among

the EMR specimens (time zero), there was only one in which the material was observed. In this sample (patient #5), the material was blue-gray with a bubbly appearance, acellular with no associated inflammatory reaction (Fig. 5). This blue-gray appearance is similar to that observed when the material from the manufacturer's container was processed for histological examination (Fig. 6). As time advances, the inflammatory response, consisting of a multinucleated giant cell reaction and proliferation of histiocytes, becomes more prominent. One example is seen in Fig. 7 (patient #2), a specimen obtained 198 days after the injection, where numerous giant cells and histiocytes proliferate along with lymphocytes, to the point that palisading granulomas are now evident as forming rosette-like formations. In another example of long-standing deposition (patient #5), the specimen obtained 36 days after the injection showed a similar granulomatous reaction. However, the Orise™ gel had lost the blue-gray or pink appearance of earlier days and was replaced by hyalinized fibrotic tissue (Fig. 8), which may indicate that the iatrogenic lesion may persist for a long time.

Discussion

In this case series, we present the histopathological findings after injecting Orise™ gel prior to EMR and the potential clinical implications of histologic changes due to the mucosal lifting material. The histological appearance varied depending on the amount of time between the injection and the examination. Immediately after the injection, the material appears basophilic (bluish), with no inflammatory infiltrates seen—in essence, similar to what is observed when the native non-injected material is examined under the microscope (Fig. 6).

In the latest version (2017) of the Clinical Guidelines of the European Society of Gastrointestinal Endoscopy, it is recommended to use products that would provide a sustained submucosal cushion compared to normal saline, and are viscous and proven to be safe in EMR procedures: for example, succinylated gelatin, hydroxyethyl starch or glycerol [3]. However, it is theoretically possible for tissue reaction and allergic side effects to occur against these lifting agent compounds. While this reaction mechanism in our cases is not entirely known, the reason may be related to the synthetic polymer, fat compounds or dyes within their content, and a reaction that forms as a result of the interactions between these compounds. While no toxicity or antigen-antibody reaction to HA has been reported in humans, the potential of contributing to the reproduction of the residual tumor cells in the resection area poses a disadvantage [4]. HMC is one of the agents used for this purpose, while this agent is also likely to potentially cause an antigen-antibody reaction [5]. To date, no significant side-effect has been reported regarding SG, whereas there is a potential for developing an allergic reaction against bovine proteins. In EMR, to delineate the lateral and deep borders of the lesion and identify deep tissue damage, the addition of biologically inert substances into lifting agents is frequently preferred, and this is recommended by the same guidelines [3]. Regarding the use of Orise™ gel, it is an inert

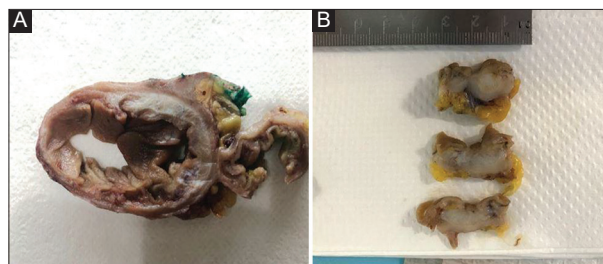


Figure 4 (A) The wall of the intestine is markedly thickened due to the penetration by Orise™ gel. (B) In another example, a nodule/mass occupies the intestine wall with extension into the adipose tissue

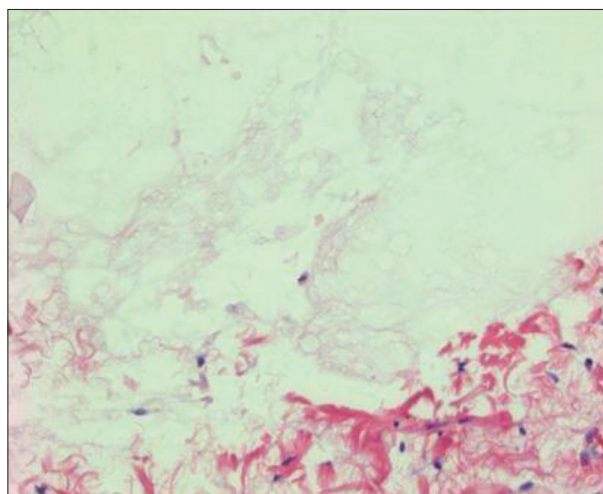


Figure 5 Example of “time zero” in the only case where Orise™ was observed histologically on the endoscopic mucosal resection specimen (hematoxylin and eosin, 200×)

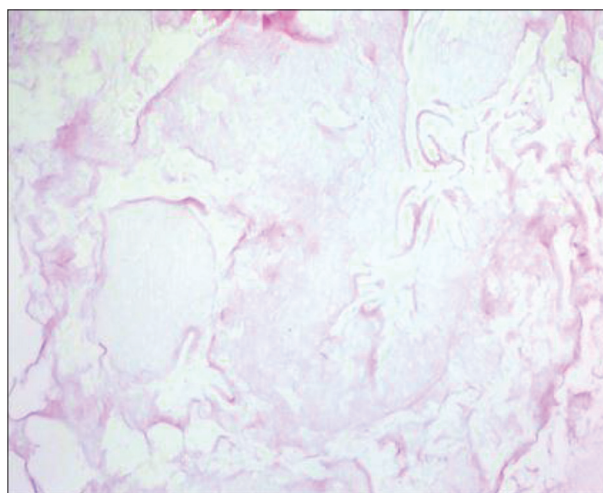


Figure 6 Orise™ gel (magnification 100×)

dye that theoretically has the potential to cause foreign body reactions.

Orise™ gel is a product that received the approval of the FDA in 2018 and has been widely used as a submucosal lifting agent for EMR and ESD procedures [6]. However, it

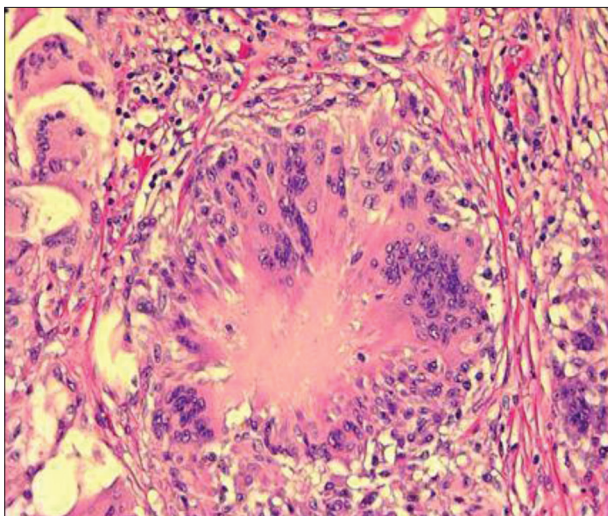


Figure 7 The reaction in the patient with the longest follow up (198 days) showed palisading of histiocytes and giant cells in a rosette-like formation (hematoxylin and eosin, 200×)

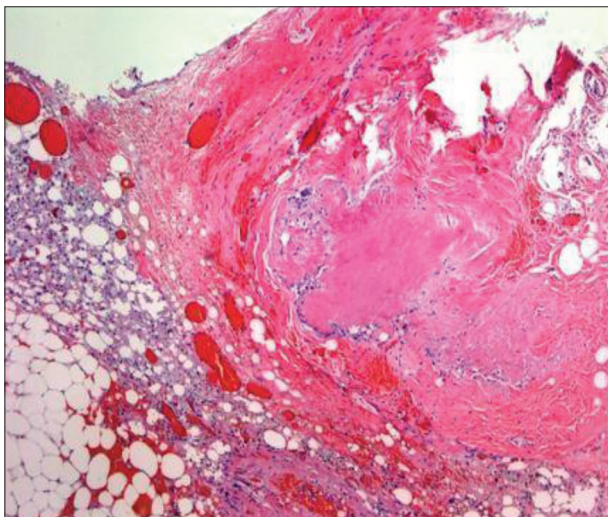


Figure 8 The patient who had a partial obstruction requiring an additional exploration and re-excision also showed fat necrosis, chronic inflammation, and giant cells surrounding hyalinized Orise™ material

was observed in our center that Orise™ gel caused a set of histopathological changes in the endoscopic and surgical specimens. In our patient cohort, it was observed that this product could remain without resorption as an amorphous acellular material. While this material showed a pale basophilic staining pattern with no inflammation on H&E staining in the early period, it gained an eosinophilic staining pattern in the late period, with multinucleated giant cell reaction. In additional examinations, as opposed to tumor-associated mucin and amyloid accumulation, the specimens were negative for Alcian blue, Periodic acid–Schiff (PAS), PAS–diastase (PAS-D) and Congo Red, and did not have the classic green birefringence.

The foreign body-related granulomatous reaction is typically characterized by a histiocytic reaction accompanying

multinucleated giant cells around the foreign material. This reaction pattern accompanying the acellular amorphous material was observed in our cohort. While granulomatous reactions have a benign nature, in tissues with thin walls, especially the intestinal structures, they can cause significant complications, such as ulceration, bleeding and even perforation [7-10]. In addition, endoscopic findings may be confused with those of inflammatory bowel diseases and other tumor-like lesions in clinical practice, leading to potential further workup, including surgical intervention. We observed that the Orise™ gel material was present beyond the *muscularis propria* into the surrounding adipose tissue of a resected segment of the intestine. In some cases, an indurated crater was observed mimicking a tumor.

Recent publications have reported similar side-effects (Table 2). In the 3 case examples presented by Cypher *et al*, it was observed that, after EMR, Orise™ gel remnants led to a histopathologically mucin-like accumulation, but this was eliminated by PAS, PAS-D, and cytokeratin negative staining [11]. In a case series containing 4 cases published by Westbrook *et al*, immediately after Orise™ gel injection, a pale, blue-grey, mucin-like appearance was observed on H&E staining, but this accumulation was mucicarmine-positive and PAS, PAS-D, trichrome, and Alcian blue-negative [12]. This study also showed that this accumulation had a different character approximately 2 months after Orise™ gel use. It had a hard, homogenous, and eosinophilic character, and there was a granulomatous lesion accompanied by robust, foreign body-type giant cell reaction with this accumulation. It showed a faint blue pattern with trichrome and amyloid staining for Congo Red was negative. Another case series by Pezhouh *et al*, including 7 cases where Orise™ gel was used, reported findings similar to those of Westbrook *et al*, with different staining patterns in the early and late periods [13]. In the early period right after injection, the lifting agent had a mild basophilic, amorphous and bubbly staining pattern, while after approximately 3 months, an accumulation with a prominent hyalinized, pink-amorphous ribbons and globules pattern continued, accompanied by a foreign body giant cell reaction and fibrosis [12]. In the largest published histologic series of Orise™ gel to date by Olivas *et al*, a total of 58 patient specimens (51 EMR and 7 ESD) were identified, of which 88% showed amorphous, pale blue-gray material in the submucosa, which was mucicarmine and PAS negative for mucin. After surgical resection, the specimens were found to have extensive deposition of dense, eosinophilic material with associated multinucleated giant cells [14]. All these findings agreed with those obtained in our study.

However, as opposed to our cohort, all the previous studies showed only submucosal involvement, whereas we observed transmural involvement of Orise™ gel, with some samples even showing extraintestinal extension. Our series indicates that Orise™ gel may create a nodule or mass-like effect, as seen in Fig. 3A, which has not been previously reported. The material can go into the serosa of the intestine and beyond the intestinal wall into the adipose tissue (patient #5). The same patient developed small bowel obstruction with a persistent transition zone at the site of the ileocolonic anastomosis, necessitating re-exploration 2 weeks later and resection of the anastomotic

Table 2 Summary of previously published literature on the use of Orise™ and histological findings

Study [ref.]	Year of Publication	Study Design	Number of patients	Study findings
Olivas <i>et al</i> [14]	2020	Case series	58	Extensive deposition of eosinophilic material with associated multinucleated giant cells. Mucicarmine and PAS negative
Castrodad-Rodríguez <i>et al</i> [15]	2020	Case report	3	Inflammatory giant cell reaction with hyalinized eosinophilic deposits. Mucicarmine negative. PAS and PAS-D were positive
Sun [16]	2020	Abstract	2	Granulomatous giant cell reaction in the submucosa and <i>muscularis propria</i>
Esnakula [17]	2020	Case report	1	Extensive deposition of an amorphous pale acellular substance resembling mucin in the submucosa. No inflammatory response present. Mucicarmine negative
Cypher <i>et al</i> [11]	2019	Case report	3	Submucosal mucin-like accumulation
Westbrook <i>et al</i> [12]	2019	Case series	4	Formation of pale, blue-grey, mucin-like substance in the submucosa. Mucicarmine positive. PAS, PAS-D negative. Interval resection showed a foreign body-type giant cell reaction
Pezhouh <i>et al</i> [13]	2020	Case series	7	Early basophilic, amorphous reaction with a late accumulation of hyalinized pink substance. Associated inflammatory giant cell reaction

PAS, periodic acid–Schiff, PAS-D, PAS–diastase

site. The resected specimen demonstrated serosal fibrosis and a focal foreign body reaction with residual Orise™ gel. It is conceivable that the Orise™ gel was not entirely removed during the first partial colectomy and potentially contributed to the small bowel obstruction in the postoperative period.

There are several limitations to our study. Firstly, the study was retrospective in nature and had a relatively small population. However, all patients included in the study had surgical specimens confirming the presence of Orise™ gel in the tissues, along with characteristic histological changes. Secondly, some patients might have presented to other hospitals for follow up after undergoing the initial EMR, but we only included patients who had follow-up surveillance procedures at our center. Thirdly, the technique of injection and amount of Orise™ gel used could have influenced the extent of changes seen in the histological specimen. Although the intent of the lifting agent is to be injected into the submucosal plane, it is possible the injection needle could have inadvertently penetrated deeper mural layers. However, all procedures were performed by experienced endoscopists who have performed over 500 EMRs. In addition, consistently with previous studies, our study demonstrates that the multinucleated giant cell reaction and proliferation of histiocytes become more prominent with time, possibly involving the deeper layers of tissue.

The granulomatous reaction that forms after the use of Orise™ gel appears to be a benign process: it is not clear whether it may eventually lead to potential complications. The mass-like lesions noted on follow-up colonoscopy can certainly be misinterpreted as a malignant recurrence of a mass lesion. This potential pitfall must be acknowledged in the future use of Orise™ gel. Further studies need to concentrate on the natural progression of these histologic changes and any related complications.

Summary Box

What is already known:

- Endoscopic mucosal resection (EMR) and endoscopic submucosal dissection are minimally invasive procedures to remove lesions from the gastrointestinal wall
- Multiple viscous fluids are available to lift the lesion during endoscopic resection, which assists in complete resection with fewer adverse events
- Orise™ gel is approved by the FDA as a lifting agent for EMR, owing to its excellent sustainable submucosal lift during endoscopic resection of the lesion; however, there are concerns over the inflammatory changes after Orise™ gel use

What the new findings are:

- Characteristic histopathological changes post-Orise™ gel include foreign body granulomatous reaction and histiocyte proliferation, often demonstrating transmural extension
- Endoscopic findings after Orise™ gel can be confused with inflammatory bowel disease or tumor-like lesions in clinical practice
- The mass-like lesions can be misinterpreted as a malignant recurrence of a lesion, leading to unnecessary surgical interventions

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