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Colonoscopy in the diagnosis and management of appendiceal disease

Yuan Gao *et al.* Colonoscopy in appendiceal disease

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Abstract

In this editorial, we comment on the article by Zhang JC *et al.* published in the recent issue of the World Journal of Gastrointestinal Endoscopy 2023; 15(12): 699-704^[1]. We focused on the understanding of appendiceal disease, and the various options for diagnosis and treatment *via* endoscopy. Some factors affecting the diagnosis and management of appendiceal diseases are also discussed. The existence of any organ has its natural rationality, and the appendix is such a magical organ. A growing number of experts and scholars have gradually come to a consensus that the appendix is not a useless evolutionary relic. There are many lymphocytes and lymph nodes in the appendix wall, which has a strong immune function, and this function is particularly important for children and adolescents. Many intestinal probiotics in the appendix are very helpful for maintaining the balance of the intestinal flora. With the continuous progress of endoscopic technology, endoscopic treatment involving preservation of the appendix has shown great advantages over surgery. In the diagnosis of appendiceal inflammation and neoplasms, colonoscopy, endoscopic retrograde appendicography (ERA) and choledochoscopy help assess conditions of the appendix. Endoscopic retrograde appendicitis therapy (ERAT), abscess drainage under colonoscopy, fenestration of abscess under colonoscopy, and endoscopic or natural orifice transluminal endoscopic surgery (NOTES) resection of appendiceal neoplasms are safe

and effective endoscopic treatments for appendiceal disease. New breakthroughs in the application of endoscopy in the appendix are expected to occur in the near future.

Key Words: Appendicitis; Appendiceal neoplasms; Colonoscopy; Endoscopic ultrasonography

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Core Tip: With the popularization of the concept of minimally invasive surgery and in-depth research on the function of the appendix, methods for preserving the appendix have emerged, and endoscopic diagnosis and treatment of appendiceal diseases have gradually become the first-line treatments. We summarize the current state of colonoscopic management of appendiceal disease, with an emphasis on reconsideration of the function of the appendix and endoscopic treatment. We also put forward our own views on how to improve the diagnosis and treatment of appendiceal diseases.

INTRODUCTION

The human appendix is a narrow, blind tube with an average length of approximately 9 cm that is located between the cecum and ileum, communicating with the intestinal cavity^[2]. It can be detected at 8 wk of gestation, and lymphoid tissue appears at 14 to 15 wk of gestation, begins to develop at 2 wk after birth, and rapidly matures within a few years^[3]. The appendix has several important functions, mainly including immune function, maintenance of intestinal microbial homeostasis and coordination between them^[4]. An increasing number of studies have shown that the role of the appendix needs to be viewed dialectically. On the one hand, the appendix can be a safe house for the gut microbiome. The excised appendix was found to contain a large number of aerobic and anaerobic bacteria, mainly *Escherichia coli* and *Bacteroides*^[5]. On the other hand, it can be called the “tonsils” of the abdomen. It is rich in a large amount of

³ lymphoid tissue, which begins to appear after birth and reaches its peak at 12-20 years of age^[4]. Because of the abundant lymphoid tissue in the appendix, it can “trap” pathogens in the early stage and then develop inflammation. It is involved in the formation of intestinal IgA-secreting cells^[6]. Epidemiological studies have also shown that appendectomy is associated with a variety of diseases, such as inflammatory bowel disease (IBD) and colon cancer, as well as cardiovascular diseases, bacterial liver abscess and systemic lupus erythematosus^[7-10]. ² Appendiceal inflammation can be divided into acute appendicitis (simple acute appendicitis, acute suppurative appendicitis, gangrenous and perforated appendicitis, and periappendiceal abscess) and chronic appendicitis. Appendiceal neoplasms can be divided into those of epithelial origin (e.g., adenoma or adenocarcinoma) and those of nonepithelial origin (e.g., neuroendocrine tumors or lymphomas)^[11, 12]. In this editorial, we discuss the current and emerging role of endoscopic management of appendiceal diseases.

RECONSIDERATION OF THE FUNCTION OF THE APPENDIX

The appendix wall consists of the mucosa layer, submucosa layer, muscularis propria layer and serosal layer. The appendix has abundant lymphoid tissue that is rich in germinal centers of B cells, lymphodendritic cells and macrophages. Many plasma cells in the lamina propria of the mucosa can produce IgA and IgG, agglutinate with pathogens, promote phagocytosis by phagocytes, and activate complement. Ig A is the major immunoglobulin in gastrointestinal-associated lymphoid tissues. The secreted immunoglobulin A (sIgA) produced by the appendix plays an important role in repairing colonic biofilms when it is destroyed^[4]. Mucosal intraepithelial lymphocytes (IELs) are composed mainly of CD8⁺ regulatory T cells and M cells and play important roles in the recognition and transport of antigens. IELs are considered to have innate immune response functions and are immune activation areas. In addition, the appendix is rich in natural killer T cells, which rapidly produce cytokines and chemokines after immune activation.

Previous studies have indicated that there are abundant and diverse microbial populations in both inflammatory and noninflammatory appendices. There are

abundant intestinal beneficial bacteria in the appendix biofilm. When the intestine loses many beneficial bacteria due to pathogen invasion, the appendix quickly participates in the reconstruction of the intestinal microecology. In 2013, Guinane *et al* conducted the first comprehensive analysis of the human appendiceal microbiota by using 16S rRNA high-throughput sequencing (HTSeq) and reported that the microbial composition was highly diverse with obvious individual differences^[13]. The hypothesis that the appendix is a reservoir of beneficial bacteria in the human body was preliminarily verified. Subsequently, more researchers have used 16S rRNA HTSeq to analyze the microbial composition of the appendix in different populations^[14, 15]. When the body is infected by pathogenic bacteria or antibiotics are applied, resulting in intestinal flora imbalance, diarrhea and other symptoms, the beneficial bacteria in the appendix cavity are released into the intestine to participate in the balanced reconstruction of the intestinal microecology^[16].

The appendix is associated with many intestinal diseases. Appendectomy is thought to be a risk factor for recurrent *Clostridium difficile* infection^[5]. However, some researchers hold the opposite view that appendectomy is not associated with recurrent *Clostridium difficile* infection^[17]. The appendix is likely to be a preventive factor for colorectal cancer^[18]. The mechanism may be related to the abundance of lymphoid tissue, immune-secreting cells and beneficial intestinal bacteria in the appendix. Appendectomy is closely related to age, the sequence of acute appendicitis and UC^[4, 19]. The incidence of UC and UC-related colectomy decreases after appendectomy in patients younger than 20 years without UC. For non-intestinal diseases, the risks of acute myocardial infarction and ischemic heart disease are related to appendectomy^[20, 21]. It is possible that the operation changes the function of the immune system, leading to an increased risk of cardiovascular disease. Appendectomy is an independent risk factor for gallstones and drug resistance in patients with biliary tract infections and is closely related to the occurrence of pyogenic liver abscess^[22-24]. Recently, large-sample cohort study has indicated that appendectomy increases the risk of autoimmune

diseases^[25]. There is clearly a correlation between appendectomy and immune inflammation.

ENDOSCOPIC DIAGNOSIS OF APPENDICEAL DISEASE

Endoscopy is helpful in the diagnosis of appendicitis. When considering inflammatory diseases of the appendix, colonoscopy allows direct observation of the opening of the appendix, helps biopsy suspicious lesions and excludes ileocecal inflammation, diverticula or tumors. Currently, endoscopic retrograde appendicography (ERA) helps the appendix located, and indirectly reflects the conditions (stenosis, dilatation, filling defect and perforation) in the lumen of the appendix^[26]. In addition, the condition of the lumen of the appendix can be observed directly, and appendix luminal biopsy can be performed *via* choledochoscopy. Endoscopic findings of acute appendicitis include deformation of the appendiceal orifice; varying degrees of congestion, edema, erosion, granularity, brittleness, or irregular shallow ulcers with yellow–white exudate on the surface; repeated stimulation of inflammation, which often leads to abnormal appendiceal contraction and relaxation, and its opening is usually in a state of continuous contraction; and obvious pain in the right lower abdomen when the appendix is touched with biopsy forceps. In addition to obvious congestion and edema at the appendiceal opening, the appendiceal abscess also showed a narrow, deformed and deviated opening, locally protruding into the intestinal cavity in a hemispherical shape and often surrounded by a raised appendiceal crease, resembling a tumor in appearance; moreover, there may be compression of the medial or posterior wall of the cecum.

The traditional diagnosis of appendiceal neoplasms relies mainly on imaging, including abdominal ultrasound, CT and MRI. Current studies suggest that when an appendiceal tumor grows into the intestinal cavity, it has a characteristic colonoscopic appearance, that is, an intraluminal bulge at the opening of the appendix. Low-grade appendiceal mucinous neoplasms generally manifest as hemisphere-like protrusions at the ostium of the appendix, with a good mucosa surface and displacement and occlusion of the ostium of the appendix. Adenocarcinoma of the appendix was characterized by rough,

erosive, stiff mucosa at the opening of the appendix and obvious oozing of blood after inflation or during biopsy. Colonoscopy and ultrasound colonoscopy can be used to evaluate the nature of the appendiceal eminence, extent of extraluminal lesions and extent of lymph node involvement before operation. Compared with the traditional diagnostic methods for appendiceal neoplasms, colonoscopy not only detects appendiceal neoplasms at an early stage but also has diagnostic value for low-grade appendiceal mucinous neoplasms and appendiceal adenocarcinoma and is highly helpful in evaluating tumor staging and performing preoperative biopsy^[3]. To improve the diagnosis and treatment of appendiceal neoplasms, additional attention should be given to obtaining a detailed history. If the patient presented with chronic right lower abdominal pain that did not disappear after treatment and could not be explained by appendicitis, sufficient attention was given to the patient, and colonoscopy was performed as much as possible. The cecum, the opening of the appendix and the end of the ileum were carefully observed during colonoscopy. Once an abnormal appendiceal opening is found by colonoscopy, biopsy should be performed as much as possible. If conditions permit, ultrasound colonoscopy should be performed.

ENDOSCOPIC TREATMENT OF APPENDICEAL DISEASE

¹ Endoscopic retrograde appendicitis therapy (ERAT) is a new and minimally invasive alternative method for the diagnosis and treatment of acute appendicitis. Liu *et al* first introduced and implemented the technique in 2012^[27]. ERAT was inspired by endoscopic retrograde cholangiopancreatography (ERCP) technology. This novel technique requires direct endoscopic imaging or fluoroscopic endoscopic retrograde appendicography (ERA) to distinguish between suspected acute appendicitis and actual acute appendicitis. For patients with uncomplicated acute appendicitis, ERAT is currently recommended, especially for patients with luminal stenosis and fecalith. The advantages of ERAT include the absence of scarring on the body surface; a reduced incidence of postoperative pain; surgical incision-related complications such as incisional hernia, incisional infection, postoperative peritoneal reaction, intestinal

adhesion, and intestinal obstruction; and the preservation of potential physiological function of the appendix.

The appendiceal abscess is a complex appendicitis, which is an abscess or inflammatory mass formed by the exudation of the appendix, the adhesion of the greater omentum and the surrounding intestinal canal. Abscess drainage under colonoscopy and fenestration of abscess under colonoscopy help in the treatment of appendiceal abscess^[28]. The advantages of stent drainage for appendiceal abscess treatment include reducing the use of antibiotics and accelerating recovery, causing relatively little trauma, and preserving the potential function of the appendix.

When ERAT or, conservative drug conservative treatment or acute complicated appendicitis such as gangrene and perforated appendicitis, the incidence of serious complications, such as acute diffuse peritonitis and sepsis will increase, and the appendix cannot be preserved, and appendectomy should be performed in time. There are several types of resection: natural orifice transluminal endoscopic surgery (NOTES), the transgastric approach, the transvaginal approach and the transcaecal approach, and appendectomy under colonoscopy. Most appendiceal neoplasms have no obvious symptoms and can manifest as symptoms and signs of acute or chronic appendicitis. Some larger cases show a mass in the right lower abdomen, which may have been accompanied by intestinal obstruction. The advantages of endoscopic or NOTES resection of appendiceal neoplasms include the absence of scars on the body surface, the presence of minimal trauma, less occurrence of postoperative complications and the significant reduction in the anesthesia burden.

SEVERAL FACTORS ASSOCIATE WITH THE DIAGNOSIS AND MANAGEMENT OF APPENDICEAL DISEASE

At present, the appendix is recognized to be closely related to immunity and thus related to some autoimmune diseases, although the mechanism has not been fully elucidated. Understanding this point can help us find a breakthrough in diagnosis when encountering atypical appendiceal disease. Combined with targeted biopsy, the diagnosis can be more precise. With the improvements in the endoscopic diagnosis and

understanding of appendiceal disease, ulcerative colitis combined with peri-appendiceal inflammation (PAI) is becoming increasingly common. The main endoscopic manifestations of PAI are appendiceal orifice inflammation (AOI) and a peri-appendiceal red patch (PARP)^[29]. Many retrospective and prospective studies have shown that the endoscopic findings of PAI are consistent with those of UC, revealing mucosal granular changes, mucopurulent changes, mucosal bleeding, mucosal friability, erosion or ulceration^[30, 31]. The local manifestations of the appendix under endoscopy are diverse and need to be distinguished and diagnosed more carefully when combined with pathological biopsy and other technical methods. A case report from Japan suggested that the endoscopic manifestations of UC combined with AOI could be similar to those of lymphoma and that extranodal marginal zone lymphoma was suspected of being gastric mucosa-associated lymphoid tissue (MALT) lymphoma, with slightly raised reddish lesions and microvascular dilatation but no erosions or ulcerations. However, flow cytometry and pathological analysis led to the diagnosis of UC with AOI^[32]. Therefore, when the above atypical manifestations are found under endoscopy, the possibility of an AOI could also be considered.

In the treatment of infectious appendiceal inflammation, antibiotics play an important role. However, self-drug resistance, intestinal microbiome changes, and recurrent appendicitis are inevitable, which poses a problem for the treatment^[33, 34]. Studies have shown that patients treated with antibiotics for the first time have a recurrence rate of appendicitis of 27.3% within 1 year and 39.1% after 5 years, after which the appendix is removed by surgery^[35]. Therefore, how to reduce the long-term recurrence rate of patients during antibiotic treatment is urgently needed. According to the current literature, the recurrence rate of simple acute appendicitis in patients treated with ERAT is lower than that in patients treated with antibiotics within 1 year^[27, 36], and the combination of ERAT and antibiotics for the treatment of simple acute appendicitis has not been considered. Although this will increase the short-term hospitalization cost, it can accelerate the recovery rate of patients and reduce the length of hospital stay, which

is beneficial in the long run. However, additional research is needed to support this evidence.

Due to the low incidence of appendiceal neoplasms, the general early clinical symptoms are atypical, and the misdiagnosis rate is high. Clinicians should pay more attention to patients with suspected appendiceal neoplasms and improve the diagnosis rate so that patients can receive effective treatment as soon as possible. Adequate preoperative evaluation is helpful for determining treatment plan and follow-up strategy. Preoperative serological examination, endoscopic examination, B-ultrasound, CT/MRI and molecular immunological examination provide effective diagnostic methods for clinicians^[37, 38]. During the operation, surgeons need to be careful to completely remove the tumor tissue during the one-stage operation, avoid destroying the localized tumor and causing abdominal implantation metastasis, and achieve negative surgical margins as much as possible. For patients with other abdominal organ metastases, additional treatment is needed according to the actual situation. Patients who are unable to undergo surgery can also receive palliative chemotherapy according to their condition. Intraoperative frozen sectioning and postoperative routine pathology are helpful for determining the type of tumor. It is worth noting that pathologists need to clearly distinguish the tissue sources of appendiceal tumors and ileocecal tumors to improve diagnostic accuracy. In the course of this disease, it is necessary to improve the perioperative management of patients with appendiceal neoplasms, reduce surgical complications, improve the survival rate, and perform good long-term follow-up to record the prognosis of appendiceal neoplasms.

CONCLUSION

In this editorial, we have summarized the current state of colonoscopic management of appendiceal disease, with an emphasis on the reconsideration of the function of the appendix and endoscopic treatment. Understanding the immune function of the appendix helps us to better understand the impact of appendiceal diseases on the overall function of the body, which also facilitates us to better identify lesions. The

combination of current powerful endoscopic or endoscopic ultrasonography methods, as well as pathological and molecular tests, can help us to accurately diagnose the lesions. In the treatment of appendiceal diseases, the patient's constitution and pathological characteristics should be fully considered, and a treatment method involving complete effect, less trauma and a good prognosis should be chosen. We are encouraged by the refinement of techniques for treating appendicitis and appendiceal neoplasms. We hope that more endoscopic research will be devoted to this tiny organ.

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