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Post-endoscopic submucosal dissection phlegmonous enteritis: A case report and literature review

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ARTICLE INFO

CelPress

Keywords: Phlegmonous enteritis Hashimoto's thyroiditis Thrombocytopenia ESD Case report

ABSTRACT

Background: This study presents the initial case of phlegmonous enteritis following endoscopic submucosal dissection (ESD), a rare and potentially fatal complication. Additionally, a comprehensive review of relevant literature is provided.

Case report: A 66-year-old female patient, diagnosed with Hashimoto's thyroiditis and thrombocytopenia, underwent ESD to address a laterally spreading tumor located in the ascending colon. After the procedure, the patient manifested abdominal pain and a high fever, was diagnosed with peritonitis, necessitating an emergency exploratory laparotomy and right hemicolectomy. Subsequent histological examination indicated a significant presence of neutrophil infiltration across all layers of the intestines. The ascites culture yielded the growth of *Escherichia coli*.

Literature review: A search was conducted in the PubMed database to identify case reports conforming to the definition of phlegmonous enteritis proposed by Rokitansky et al. We retrieved about 30 studies regarding phlegmonous enteritis from 1951 to 2022, with around 39 cases. Among these, only 28 patients had comprehensive medical data available. Subsequently, an examination of the literature was undertaken to explore the pathogenesis, prevention, and treatment of phlegmonous enteritis.

Conclusion: The possibility of phlegmonous enteritis should be taken into consideration in cases of unexplained acute abdomen, particularly in patients with compromised immunity, in order to provide active surgical and antibiotic interventions.

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https://doi.org/10.1016/j.heliyon.2023.e23467

Received 11 July 2023; Received in revised form 30 November 2023; Accepted 5 December 2023

Available online 9 December 2023

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1. Introduction

Endoscopic submucosal dissection (ESD) has emerged as a safe and minimally-invasive approach, offering a promising therapeutic option for early gastrointestinal cancer [1–4]. While hemorrhage and perforation represent the prevailing complications associated with ESD, they can be effectively managed non-surgically in the majority of instances [5]. Notably, the occurrence of other severe complications remains sporadic. Phlegmonous gastritis following gastric ESD has been reported as a rare complication by Hironari Ajibe et al. and Lee et al. [6,7]. To the best of our knowledge, there have been no reports of phlegmonous enteritis following colon ESD.

Phlegmonous enteritis, a rare yet potentially lethal condition resulting from pyogenic bacterial infections [8], can lead to hematogenous dissemination, triggering bacteremia and sepsis. This study presents the inaugural case of phlegmonous enteritis as a secondary consequence of ESD. Despite initial antibiotic treatment, the patient ultimately required emergency surgery. Phlegmonous enteritis represents a grave complication of ESD, necessitating heightened awareness and monitoring in immunocompromised patients.

1.1. Case presentation

A 66-year-old female patient presented at our hospital seeking endoscopic submucosal dissection (ESD) for a laterally spreading tumor located in the ascending colon near the hepatic flexure. The patient had been prescribed Euthyrox for an extended period of time due to hypothyroidism caused by Hashimoto's thyroiditis (HT). Additionally, the patient had consistently shown leukocytopenia and thrombocytopenia in routine blood tests over the years. A routine blood test conducted at our hospital revealed a leukocyte count of $3.16 \times 10^{\circ}$ /L and a platelet count of $109.00 \times 10^{\circ}$ /L. The patient did not exhibit any other symptoms. Furthermore, no significant abnormalities were detected in cardiac enzymes or blood coagulation.

The patient underwent ESD with general anesthesia and tracheal intubation. The procedure was successfully executed without any instances of intraoperative bleeding or injury to the muscle layer. To enhance visibility and facilitate the dissection, a submucosal injection of normal saline (NS) combined with sodium hyaluronate and methylene blue was administered, resulting in a positive lifting sign. We found a laterally developing pink colon adenoma endoscopically (Fig. 1A). A circumferential incision measuring 0.5 cm was made along the outer edge of the mass using the Daul knife. Subsequently, submucosal dissection was performed, leading to the successful removal of the mass (Fig. 1B). After the operation, electrocoagulation was employed as a preventive measure against hemorrhaging in the exposed blood vessels within the wound. Subsequently, meticulous cleaning and monitoring of the wound were



Fig. 1. The endoscopic treatment of colon adenoma. (A) The identification of a lateral developmental type, pink, prior to resection. (B) A circumferential incision measuring 0.5 cm was made along the outer edge of the mass, followed by submucosal dissection and subsequent removal of the mass. (C)The postoperative specimen measured 1.8×1.5 cm and the tumor was sent for pathologic evaluation. (D) Closure of the incision was achieved through the continuous application of 13 metal wound clips.

conducted to identify any signs of bleeding or discharge. The postoperative specimen measured 1.8×1.5 cm and was subsequently submitted for pathological evaluation (Fig. 1C). The incision was consistently secured using 13 metal wound clips (Fig. 1D). After the ESD operation, the patient was also started on anti-infective with cefoperazone sulbactam and nutrition support therapies.

Four hours post-procedure, the patient experienced intermittent abdominal pain and occasional nausea unaccompanied by vomiting or fever. Physical examination showed tenderness in the right abdomen, devoid of rebound tenderness and muscular tension, while bowel sounds remained within normal limits. Symptomatic analgesic treatment successfully alleviated the symptoms. However, 9 h following the operation, the patient experienced a recurrence of right abdomen pain, which subsequently progressed to involve the entirety of the abdomen. The patient exhibited persistent nausea without vomiting and reported a perceived increase in body temperature. Upon physical examination, diffuse tenderness with rebound tenderness, primarily in the right abdomen, was noted. Dullness to percussion was observed, while pain during percussion in the liver area was absent. Shifting dullness to percussion was also negative, and normal bowel sounds were detected. The patient's maximum body temperature was recorded as 37.8 °C. An emergency abdomen CT scan revealed edematous thickening of the intestinal wall in the ascending colon, accompanied by peripheral exudative changes. No signs of intestinal perforation or obstruction were identified. The results of the routine blood test and C-reactive protein (CRP) indicated a CRP level of 2.45 mg/L, a white blood cell (WBC) count of $3.43 \times 10^{\circ}$ JL, a neutrophil percentage of 85.40%, a lymphocyte percentage of 9.40%, an absolute value of lymphocytes of 0.32×10^{9} /L, and a platelet (PLT) count of 79.00×10^{9} /L. Additionally, the procalcitonin (PCT) level was measured at 0.58 ng/ml. The patient was diagnosed with peritonitis. As a result, the antibiotic treatment was upgraded from cefoperazone sulbactam to a combination of cefoperazone sulbactam and ornidazole. Despite these interventions, the patient's condition continued to deteriorate without any noticeable improvement, prompting us to seek a consultation.

A consultation was attended by a Multi-disciplinary Treatment (MDT) team comprising physicians specializing in gastroenterology, abdominal surgery, and imaging departments. In light of the patient's presentation of acute abdominal pain following an endoscopic submucosal dissection (ESD), potential etiologies such as gastrointestinal perforation, post-ESD serositis, and intestinal obstruction should be taken into account. Despite the absence of perforation on the abdominal CT scan, a reassessment was deemed necessary to ascertain the possibility of delayed perforation. Upon CT re-examination, it was observed that the anterior wall of the ascending colon exhibited distension caused by the presence of gas. Furthermore, exudation was identified in the subserosa of the middle section of the ascending colon. Additionally, a small quantity of ascites was observed (Fig. 2A). Subsequently, 18 h following the procedure, the patient experienced an accelerated heart rhythm, reduced blood pressure, peritonitis, and septic shock. Consequently, emergency surgical exploration was undertaken.

After tracheal intubation and under general anesthesia, a colonoscopy was performed. The ESD site in the ascending colon showed no apparent perforation, with the metallic wound clips effectively sealed. Nevertheless, the adjacent intestinal areas demonstrated signs of edema and constriction (Fig. 2B). The endoscope successfully traversed. The laparoscopy revealed the presence of approximately 100 ml of intra-abdominal purulent exudates concentrated in the right paracolic gutter, which were collected for bacterial culture. The ascending colon exhibited significant edema and wall thickening. The anterior wall was encrusted with pus, and subsequent cleaning revealed the presence of gangrene. Given the intricate medical circumstances, the decision was made to transition to laparotomy and proceed with a right hemicolectomy. After the surgery, the patient returned to the ward and was instructed to fast from both solids and liquids. She was also started on anti-infective with moxifloxacin injection and nutrition support therapies.

The examination of resection specimens revealed the presence of edema in all layers of the intestinal wall, with a predominant thickening and edema in the submucosa (Fig. 3A). The muscle layer of the ESD wound remained intact without any perforation (Fig. 3B). Under microscopic analysis, all layers of the intestinal wall exhibited diffuse infiltration of neutrophils, along with the



Fig. 2. Prior to laparoscopy exploration, we conducted a re-examination using computed tomography (CT) and assess the endoscopic findings. (A) Upon CT re-examination, it was observed that the anterior wall of the ascending colon exhibited distension caused by the presence of gas. Moreover, exudation was detected in the subserosa of the middle segment of the ascending colon. Additionally, a small amount of ascites was noted. (B) An enteroscopy was performed, revealing no evident perforation at the ESD site of the ascending colon, with well-closed metal wound clips, the peripheral intestines had edema and were narrow.



Fig. 3. The gross and microscopic observations of the excised specimen. (A) The examination of resection specimens revealed the presence of edema throughout all layers of the intestinal wall, with a notable prevalence of thickening and edema specifically in the submucosa. (B) The muscle layer of the ESD wound remained intact without any perforation. (C) The histological analysis of the resection specimen demonstrated extensive neutrophil infiltration across all layers of the intestinal wall, resulting in the formation of multiple abscesses (haematoxylin and Eosin [H&E]).

presence of abscesses (Fig. 3C). Bacterial colonies were observed in the submucosa surrounding the ESD lesion, and no thrombosis was detected in the mesenteric vessels, leading to a diagnosis of phlegmonous enteritis.

The ascites culture revealed the presence of *Escherichia coli*, which was found to be negative for extended-spectrum β -lactamase enzymes through susceptibility experiments. Based on the results of drug sensitivity tests, the patient was treated with moxifloxacin, a sensitive antibiotic, as part of anti-infective therapy. Following a 10-day hospital stay without any surgical complications, the patient was discharged and subsequently experienced a successful recovery during the 32-month follow-up period.

2. Literature review and discussion

2.1. Method

In order to ascertain previously documented instances of phlegmonous enteritis, a comprehensive search was conducted on the PubMed database utilizing the search terms "Phlegmonous inflammation," "phlegmonous enteritis," "phlegmonous colitis," and "phlegmon." Furthermore, the references cited in previously published reports were thoroughly examined. The inclusion criteria encompassed case reports, case series, and other descriptive studies. Additionally, the references cited in previously published reports were also scrutinized.

2.2. Definitions

Gastrointestinal phlegmon is an infrequent yet potentially fatal ailment that typically presents with acute abdominal pain and elevated body temperature [9–11]. The pathological characteristics encompass widespread purulent inflammation, primarily affecting the submucosal layer [8,11–14]. The inflammatory process may extend to the serosal surface, leading to the development of peritonitis

Table 1

A comprehensive tabular representation of pertinent clinical information pertaining to patients diagnosed with phlegmonous enteritis in the literature.

Author	Study date	Age	Sex	Segment(s) of intestine involved	Comorbidities	Bacterial culture	Outcome
Rowlands Kellaway	1951 1963	40 67	F M	Small intestine: ileum Colon: sigmoid	Strangulated hernia Aortosclerosis, dissection of aorta, constitution	Not done Not done	Survival Death
Gerard	1969	38	М	Colon: sigmoid, rectum	Alcoholism, fatty liver disease	Gram-negative rods (Escherichia coli)	Death
Mendeloff and Wenger	1975	49	М	Colon: the whole colon	Alcoholism	Gram-negative rods (Escherichia coli)	Death
Rosen and Won	1978	43	Μ	Colon: ascending to transverse colon	Alcoholism, cirrhosis, severe fatty liver disease	Gram-negative rods, type unspecified	Death
	1978	30	М	Colon: caecum	Cirrhosis, ischemic enterocolitis	Gram-positive rods, type unspecified	Survival
	1978	61	F	Small intestine and colon: ileum and left colon	Alcoholism, cirrhosis	Gram-positive rods, type unspecified	Death
	1978	29	М	Small intestine: duodenum	Alcoholism, leukemia, bacterial endocarditis	Gram-positive cocci, type unspecified	Death
	1978	83	М	Small intestine: jejunem	Severe fatty liver disease	Not done	Death
	1978	64	М	Small intestine: jejunem	Alcoholism, severe fatty liver disease	Gram-negative rods, type unspecified	Death
	1978	42	F	Small intestine: site unspecified	Cirrhosis, alcoholic hepatitis	Not done	Death
	1978	60	М	Small intestine: site unspecified	Alcoholism, cirrhosis, alcoholic hepatitis	Not done	Death
Kneafsey et al.	1987	58	М	Small intestine: duodenum	Hypercalcinemia, multiple myeloma, renal failure	Gram-positive cocci (<i>Streptococci</i>)	Survival
Ito et al.	1991	52	М	Small intestine: ileum	Alcoholism, fatty liver disease	Rare Gram-negative rods, type unspecified	Death
Brooks and Madsen	1991	73	F	Small intestine: ileum	Atherosclerosis	Gram-negative rods (Klebsiella pneumoniae)	Survival
Reyes Gutiérrez et al.	1992	53	F	Colon: the whole colon	Cirrhosis	Gram-positive cocci (Streptococci pneumoniae)	Death
Mooney et al.	1997	69	М	Small intestine: jejunem	Appendicitis, carcinoma of colon, operation on prostate, hypertension, hypercholesteremia, ischemic cardiomyopathy	Gram-negative rods, type unspecified	Survival
Svane	2000	61	Μ	Small intestine: jejunem	Squamous cell lung carcinoma, angina pectoris	Gram-positive cocci (<i>Streptococci</i>)	Survival
Namkung et al.	2001	65	Μ	Colon: ascending colon, caecum	Carcinoma of colon, congestive heart failure	Gram-negative rods (<i>Escherichia coli</i>)	Survival
Holzer et al.	2009	43	М	Colon: midascending to midtransverse colon	Cirrhosis	Gram-positive cocci (Enterococcus faecalis)	Survival
	2009	70	М	Colon: the whole colon	Cirrhosis, C hepatitis, diabetes	Gram-positive cocci (Enterococcus, Bargen's streptococci)	Survival
	2009	69	М	Colon: the whole colon	Cirrhosis, diabetes	Gram-positive cocci (Streptococci)	Death
Bang et al.	2014	60	Μ	Colon: sigmoid	Carcinoma of colon	Not done	Survival
Matsumoto et al.	2015	74	М	Small intestine: duodenum	Myelofibrosis, multiple myeloma	Gram-positive rods (Bacillus thuringiensis)	Survival
Gilbert and Byard	2018	52	М	Colon: ascending colon, caecum	Cirrhosis, alcoholism, metamorphosis	Gram-negtive rods (Escherichia coli)	Death
Garland and Tse	2018	40	М	Small intestine: duodenum	Cirrhosis, alcoholism, Diabetes, hypertension, pancreatitis, stenosis of bile duct	Not done	Death
Pisipati et al.	2020	59	М	Colon: ascending colon	C hepatitis, cirrhosis, alcoholism	Gram-negtive rods (Campylobacter coli)	Survival
Lajevardi et al.	2020	70	F	Small intestine: jejunem	Hysterectomy, cholecystectomy	Gram-positive cocci (Streptococci)	Survival

and sepsis, which are challenging to diagnose without the use of laparotomy or postmortem examination [8,11–15]. The initial description of phlegmonous enteritis was provided by Rokitansky et al., in 1842 [16].

2.3. Search results

We reported the first case of colonic adenoma with a sporadic and severe post-ESD complication: phlegmonous enteritis. The initial documentation of phlegmonous enterocolitis was presented by Rokitansky et al., in 1842 [16]. Despite the abundance of literature on phlegmonous gastritis, it was not until 1969 that Gerard PW discovered merely two comprehensive analyses of phlegmonous enteritis in the English literature, encompassing a total of 34 cases. These cases comprised 8 instances reported by MacCullum in 1906 and 26 cases reported by Irwin and McDonald in 1932 [14]. However, the unavailability of the original text can be attributed to the antiquity of the literature. A total of 30 studies pertaining to phlegmonous enteritis were procured from the PubMed database, spanning the years 1951–2022, encompassing approximately 39 cases. Out of these, only 28 patients possessed comprehensive medical records. The particulars of these 28 cases have been succinctly presented in Table 1 and expounded upon subsequently.

2.4. Age, sex, and segment(s) of intestine involved

The study consisted of a sample size of 28 individuals, with a male-to-female ratio of approximately 4:1. The age was 29–81 (mean 56 years old). Among the cases examined, 14 individuals exhibited involvement solely in the small intestine, with 5 cases in the duodenum, 3 in the jejunum, 4 in the ileum, and 2 with uncertain locations. Additionally, 13 cases exclusively displayed involvement in the colon, with 5 in the ascending colon, 1 in the caecum, 3 in the sigmoid colon, and 4 in the entire colon. Lastly, one case demonstrated involvement in both the small intestine and colon, specifically in the ileum and left colon. Hence, this particular ailment is commonly observed among individuals in the middle-aged and elderly demographic, with a higher prevalence in men as compared to women. The predilection sites were the small intestine and then the colon.

2.5. The etiology and pathogenesis of phlegmonous enteritis

The etiology and pathogenesis of phlegmonous enteritis remain uncertain in academic literature. While the association between phlegmonous enteritis and different liver diseases is infrequently documented, it is sufficiently substantiated by several studies [8,9, 11–14,17,18]. Additional uncommon predisposing factors include autoimmune disease (AID) [19], colon carcinoma [10,20], congestive heart failure (CHF) [20], and diabetes mellitus [9,13], among others. Out of the 28 cases examined, 11 exhibited liver cirrhosis, 11 had a history of chronic alcohol abuse, 5 presented with medium-severe fatty liver disease, 3 had diabetes mellitus, 1 had kidney failure, and 1 had thrombocytopenia. Phlegmonous gastritis following gastric ESD has been reported as a rare complication by Hironari Ajibe et al. and Lee et al. [6,7]. To the best of our knowledge, this study presents the initial case of phlegmonous enteritis following ESD.

2.6. The etiologic agents of phlegmonous enteritis

Bacterial strains were obtained from the ascites of patients diagnosed with phlegmonous enteritis. Out of the total 28 cases, bacteria were successfully isolated from either blood or ascites in 21 instances. Among these cases, 11 exhibited Gram-positive bacteria, 10 displayed Gram-negative bacteria, while the remaining 7 cases did not yield any bacterial cultures. In our specific case, *Escherichia coli* was isolated from the ascites sample.

These microorganisms are believed to be pathogens; however, the mechanisms of pathogenesis and the means by which pathogens gain access to the mucosa remain inconclusive. The theory of mucosal injury posits the potential for pathogens to penetrate the submucosa, yet the majority of the 28 cases exhibited intact intestinal mucosa. In this case, the muscle layer was intact in the ESD wound without perforation. Another possible interpretation posits that hematogenous dissemination facilitates the transmission of extra-gastrointestinal infections to the intestinal mucosa. However, it is worth noting that the majority of cases did not present with additional infective foci outside the gastrointestinal tract, such as teeth or tonsils. Consequently, this theory also faces scrutiny. Certain scholars argue that systemic diseases may contribute to an increased susceptibility to bacterial infection. Renal insufficiency, liver cirrhosis, autoimmune disease (AID), cancer, and alcoholism have been identified as predisposing factors in the literature [11,21,22]. The presence of liver cirrhosis or alcohol abuse has been found to elevate intestinal mucosa permeability, leading to a compromised anti-inflammatory response by local inflammatory cells and rendering the intestinal mucosa more susceptible to pathogenic invasion.

Escherichia coli is classified as an opportunistic pathogen, capable of inducing diseases in instances of dysbiosis within the flora, compromised immunity, or invasion of extraintestinal tissue by the bacteria. In the present scenario, the patient presented with concurrent thrombocytopenia and compromised immunity, in addition to a history of HT. The extent of her susceptibility to phlegmonous enteritis remains uncertain. Limited research exists on the association between thrombocytopenia and HT. The majority of the studies reviewed consist of case reports that demonstrate a concurrent or reciprocal causal relationship between the two conditions, suggesting a strong association [23–25]. Thrombocytopenia has been found to be linked with compromised immune function, as evidenced by its prevalence among sepsis patients [26]. Furthermore, the severity of thrombocytopenia has been positively correlated with the severity of sepsis [26]. It was reported that a patient with end-stage renal disease developed thrombocytopenia, and phlegmonous gastritis occurred after ESD surgery [6]. Total gastrectomy was required in the end. Therefore, we should be

alert to the risk of developing phlegmon in patients with thrombocytopenia after ESD.

2.7. How do we prevent post-ESD phlegmonous enteritis?

The intestinal tract serves as a habitat for bacteria, making it susceptible to postoperative infection following endoscopic biopsy, endoscopic mucosal resection (EMR), or ESD, particularly in cases of mucosal injuries. However, it is important to note that the incidence of bacteremia is significantly low. By way of illustration, in a study conducted by Byung-Hoon Min et al., only one out of forty patients (2.5%) who underwent ESD exhibited bacteremia associated with EMR or ESD [27]. Similarly, Lee TH et al. observed that bacteremia occurred in only two out of thirty-eight cases (5.3%) of upper gastrointestinal tract EMR [7]. This serves as a reminder that the utilization of prophylactic antibiotics is superfluous for standard endoscopic biopsy, EMR, or ESD procedures. Nevertheless, the appropriateness of their implementation in the high-risk demographic necessitates further validation through empirical evidence.

2.8. Diagnosis and treatment of phlegmonous enteritis

The acute abdominal pain and fever are the primary clinical manifestations of phlegmonous enteritis, making preoperative diagnosis challenging. In this study, all 28 patients were diagnosed through exploratory laparotomy or autopsy. Diagnostic techniques such as endoscopy, Endoscopic Ultrasound (EUS), and CT scans have proven to be valuable in identifying this disease.

Untreated phlegmonous enteritis is associated with a grim prognosis, leading to patient mortality within a few days. Prior to the discovery of antibiotics, mortality rates were extremely high, as evident from the literature. For instance, in a review by Gerard PW [14] 33 out of 35 patients died. Even after the advent of antibiotics, our literature review showed a significant mortality rate, with 15 out of 28 cases resulting in death—a rate of 54%. The majority of patients succumbed to sepsis or multiple organ failure. Timely laparotomy and administration of broad-spectrum antibiotics are imperative for the effective management of acute abdomen [9,28].

3. Conclusion

Phlegmonous enteritis is a relatively uncommon yet highly fatal condition characterized by an elusive etiology and pathogenesis, typically detected through laparotomy or post-mortem examination. Clinically, patients with phlegmonous enteritis present with acute abdominal symptoms that frequently progress to peritonitis and sepsis. Pathologically, the disease is characterized by diffuse suppurative inflammation, primarily affecting the submucosa, and potentially extending to the serosal surface. In this academic report, we present a case study of a 66-year-old female patient with hypertension (HT) and thrombocytopenia who experienced the development of phlegmonous enteritis following colon ESD. Additionally, we provide a concise overview of the existing literature on the pathogenesis, prevention, and treatment of phlegmonous enteritis. Given the growing prevalence of the ESD technique, it is plausible that the occurrence of this uncommon complication may rise. Therefore, it is imperative to contemplate the potential occurrence of phlegmonous enteritis in cases of unexplained acute abdomen, particularly in patients with compromised immunity, in order to provide active surgical and antibiotic interventions.

Ethics approval and consent to participate

This study adhered to the Declaration of Helsinki, and therefore, formal approval was not deemed necessary. The patient willingly provided written informed consent to participate in the study.

Consent for publication

The patient provided written informed consent for the publication of any potentially identifiable images or data included in this article.

Funding

This work was supported by the Natural Science Foundation of Liaoning Province (Grant No. 2022-MS-332).

Data availability statement

The original contributions presented in the study are included in the article. Further inquiries can be directed to the corresponding author.

CRediT authorship contribution statement

Hui Tian: Writing – original draft, Conceptualization. Pengchao Fan: Writing – original draft, Conceptualization. Fuwen Luo: Formal analysis. Chunmeng Jiang: Formal analysis. Kun Guo: Data curation. Najin Gu: Data curation. Jie Lu: Data curation. Jiawen Luo: Formal analysis. Zhiguo Wang: Writing – review & editing. Chengjuan Xing: Writing – review & editing, Supervision, Project administration, Funding acquisition.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

The authors express their gratitude to the members of their research group for their valuable contributions to the discussions.

Abbreviations

- ESD Endoscopic submucosal dissection
- EMR Endoscopic mucosal resection
- HT Hashimoto's thyroiditis
- WBC White blood cell count
- PLT Platelet count
- CRP C-reactive protein
- CT Computed tomography
- MDT Multi-disciplinary Treatment
- AID Autoimmune disease
- CHF Congestive heart failure
- EUS Endoscopic Ultrasound

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