Endoscopic submucosal dissection for silent gastric Dieulafoy lesions mimicking gastrointestinal stromal tumors

Report of 7 cases—a case report series

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Abstract
Background: Dieulafoy lesion is a rare but serious cause of gastrointestinal hemorrhage. However, some cases can be occasionally found without bleeding during the endoscopic screening, and the management remains unclear. The aim of this article was to report the efficacy and safety of endoscopic submucosal dissection (ESD) for silent gastric Dieulafoy lesions, which presented as protrusion lesions mimicking gastrointestinal stromal tumors (GISTs).

Methods: Data from the patients with gastric protrusion lesions who underwent ESD from September 2008 to April 2016 in General Hospital, Tianjin Medical University, China were recorded. Seven cases with pathological diagnosis of Dieulafoy lesion without bleeding were enrolled for further analysis.

Results: A total of 7 patients (2 males and 5 females) with mean age of 57.7 ± 4.15 years were pathologically diagnosed as Dieulafoy lesion. Four of the lesions were located in gastric antrum, 2 in the fundus, and 1 in the body of stomach, respectively. The mean sizes of the Dieulafoy lesions under white light endoscopy and endoscopic ultrasonography (EUS) were 1.06 ± 0.28 and 0.84 ± 0.29 cm. The origins of these lesions were submucosa (6/7, 85.7%) and muscularis propria (1/7, 14.3%). Three of them appeared with mixed echo under EUS, 3 with hypoechoegenicity, and 1 with hyperechogenicity. En bloc complete resection was achieved in all the lesions by ESD with average time of 76.0 ± 16.86 minutes, and no intraoperative bleeding happened. In addition, all patients were followed up for 1 to 53 months, and no recurrence or long-term complications was observed.

Conclusion: Therefore, ESD can be an effective and safe treatment for silent gastric Dieulafoy lesions with clinical presentations of submucosal protrusion lesions mimicking GISTs.

Abbreviations: APC = argon plasma coagulation, CT = computed tomography, ESD = endoscopic submucosal dissection, EUS = endoscopic ultrasonography, GI = gastrointestinal, GISTs = gastrointestinal stromal tumors, SMA = smooth muscle actin.

Keywords: Dieulafoy lesion, endoscopic submucosal dissection, gastrointestinal stromal tumor, submucosal protrusion lesions

1. Introduction
Gastric vascular malformation is an infrequent occurrence accounting for 1% to 2% of the upper gastrointestinal (GI) hemorrhage and can be distributed throughout the GI tract. Dieulafoy lesion, gastric antral vascular ectasia, and telangiectasia are the most common subsets of gastric vascular malformation and about 75% Dieulafoy lesions are found in the stomach. Dieulafoy lesion is often defined as a tortuous, submucosal artery with large caliber which can penetrate the mucosa through a solitary, round mucosal defect over time and rupture spontaneously, causing intermittent or lethal bleeding. Due to its insidious onset, minute size, and unrelated with surrounding ulcer or inflammation, it is difficult to diagnose accurately by standard methods, such as barium and endoscopic investigation, especially when no hemodynamic instability happens. Some alternative methods such as endoscopic ultrasound and computed tomography (CT) scan were reported to have a significant assist in increasing the diagnostic rate of Dieulafoy lesions. Endoscopic therapies such as hemoclips, band ligation, injection therapies, and argon plasma coagulation (APC) are the primary treatment for acute bleeding Dieulafoy lesions with primary hemostasis rate of 75% to 100%. Therapeutic angiography and surgery also participate in the treatment of bleeding Dieulafoy lesions. However, some cases may be missed before they present bleeding symptoms. Before penetrating the mucosa, the twisted arteries of silent Dieulafoy lesions may be buried in mucosa and present as protrusion lesions mimicking gastric submucosal tumors such as...
gastrointestinal stromal tumors (GISTs). Considered the difficulty to diagnose and the potential to cause lethal GI bleeding, there is an urgent need for physicians to realize and handle the Dieulafoy lesions in early stage in order to reduce the hemorrhage incidence and mortality rate. Recently, with the rapid development of endoscopic technology, endoscopic submucosal dissection (ESD), with the advantages of higher completed resection rate and more accurate pathological estimation, has been a broad accepted method for treatment of GI early neoplastic lesions and submucosal tumors. Thus, the present article reported some cases of silent Dieulafoy lesion mimicking GIST that safely and efficiently was removed by ESD.

2. Methods

2.1. Patients

We retrospectively reviewed our endoscopic database of all patients who underwent ESD for gastric submucosal protrusion lesions at the Digestive Endoscopy Center of General Hospital, Tianjin Medical University, China from September 2008 to April 2016. The patients with no bleeding symptom and pathological diagnosis of Dieulafoy lesion were selected. The demographic and pathological information of the included patients were further collected, including age, gender, lesion size, location, time of the operation, and pathological data.

The study was approved by the Institutional Review Board and Ethical Committee of General Hospital, Tianjin Medical University, China. Written informed consent for ESD was obtained from all the patients before the procedure. Preoperative endoscopic ultrasonography (EUS) and abdominal CT scan were performed to determine the size, echogenicity, origin, and the anatomical structure in the vicinity of the lesions.

2.2. Preoperative EUS

The characteristics of the common submucosal epithelial tumors are as follows: GIST always originates from muscularis propria or muscularis mucosa and presents as round average hypoechoic lesions with smooth border, leiomyoma presents as hypoechoicity with clear border and always arises from muscularis propria or muscularis mucosa, lipoma commonly arising from submucosa always shows even high echo with smooth border, and vascular lesion shows low echo or high echo and sometimes has color Doppler flow signal.

2.3. ESD procedure

All the patients were fasting for more than 8 hours before operation, and vital signs were continuously monitored during the procedure. All ESDs were performed with a single-channel gastroscope (GIF-H260, Olympus, Tokyo, Japan), under mechanically ventilated general anesthesia. A transparent cap (MH-593, Olympus) was attached to the tip of the gastroscope to provide direct views of the operation. After identifying the target lesion, some marked dots were made surrounding its margin by argon plasma coagulation (APC300, ERBE, Tuebingen, Germany). A mixture solution of glycerin fructose and methylene blue plus 1:10,000 epinephrine was injected into the submucosa at the proximal end of the target lesion via an injection needle (NET 2522-G4, Endo-Flex GmbH, Voerde, Germany) to elevate the mucosa. Then, an initial circumferential incision was performed by a hook knife (JET2, ERBE, Tuebingen, German) along the marked dots to remove the superficial mucosa. Subsequently, submucosal insertion of the tip of an insulation-tipped knife (KD-611L, Olympus) or a hook knife was used to dissect the connective tissue gradually and makes a circular incision around the lesion to expose it completely. To confirm a macroscopic resection, the surrounding connective tissue was dissected carefully, and the target lesion was removed at the root via an electro surgical knife. During the dissection, hot biopsy forceps (NE6122-G, Endo-Flex GmbH), clips (HX-610-135L, Olympus), or APC was necessarily used to coagulate all visible vessels and stop any bleeding. Several clips were used to completely close the wound to reduce the risk of perforation. If the perforation or bleeding was too severe to control with endoscope, surgery was necessary. One-piece resection was defined as the absence of any tumor remnant under endoscope after resection. Moreover, snares (NOE 342217-G, Endo-Flex GmbH), high-frequency generator (ICC-200, ERBE, Tübingen, Germany), and grasping forceps (FG-8U-1, Olympus) were also used during the operation.

After the procedure, patients were given GI decompression and fasting for 1 to 3 days with parenteral alimentation and proton-pump inhibitor treatment to prevent postoperative hemorrhage and perforation.

2.4. Pathological examination

All cases diagnosed with Dieulafoy lesion were reevaluated by an experienced pathologist (DW). Hematoxylin and eosin staining and immunohistochemistry staining were used for histopathological evaluation and classification. A Dieulafoy lesion describes a histologically normal artery which has an abnormally large diameter, maintaining a constant width of 1 to 3 mm. It runs a tortuous course within the submucosa and has no findings of vasculitis, atherosclerosis, or aneurysm. Immunohistochemical analysis of smooth muscle actin (SMA), desmin, CD117, CD34, CD31, Dog-1, Ki-67, and S-100 markers was performed in all 6 specimens. Positive reactions for CD117, DOG-1, Ki-67, and CD34 were used for the diagnosis of GISTs. Those lesions positive for S-100 were diagnosed as neurogenic tumor. Positive for SMA and desmin represented the smooth muscles. Positive CD34 and CD31 supported the diagnosis of artery.

2.5. Follow-up evaluation

All patients were followed up regularly. In order to monitor the recovery of the wound and exclude any bleeding or lesion, residual or recurrence standard endoscopy after the initial operation was performed in the first, sixth, and 12th month, respectively. If none of the conditions mentioned above happened, the endoscopy could be conducted yearly. Lesion residual is defined as lesion at the site of previous excision. Recurrence is referred to a new lesion after at least 1 negative follow-up endoscope. EUS and abdominal CT scan should be done if lesion residual or recurrence occurred.

2.6. Statistical analysis

All statistical analyses were performed using SPSS 19.0 (Chicago, IL) for Windows. Means and standard deviation were calculated for continuous variables.
3. Results

3.1. Demographics and clinical features

Seven patients (2 males and 5 females) were finally pathologically diagnosed as Dieulafoy lesion. The majority of these patients had abdominal discomfort (3/7, 42.8%), following abdominal distension (2/7, 28.6%), epigastric pain (1/7, 14.3%), and acid reflux (1/7, 14.3%). The mean age of patients with Dieulafoy lesion was 57.7 ± 4.15 years (range 51–64 years). The mean size of Dieulafoy lesions under white light endoscopy and EUS was 1.06 ± 0.28 and 0.84 ± 0.29 cm, respectively. The most frequent locations of these lesions were the gastric antrum (4/7), following the fundus of stomach (2/7, 1 of them was near the cardia) and the greater curvature of body of stomach (1/7). According to EUS, 3 of them appeared with mixed echo, 3 with hypoechogenicity, and 1 with hyperechogenicity. One of the lesions originated from muscularis propria and 6 from submucosa. Before the ESD procedure, all the cases were diagnosed as suspected GIST. The demographic and clinical data were listed in Table 1.

3.2. Therapeutic outcomes and complications of ESD

Figure 1 showed the characteristic of gastric silent Dieulafoy lesion under white light gastroscopy and EUS. All the 7 lesions were completely removed by ESD. The time for the operation was measured from the time point of marking the area to the resection of the lesion. The mean time of the operation was 76.00 ± 16.86 minutes (range 20–98 minutes). During the operation, no perforation, episode of Dieulafoy lesions rupture or bleeding, procedure-related significant bleeding, or other severe intraoperative complications happened. The key steps of ESD were shown in Fig. 2. During hospitalization, no patient had other significant complications such as early post-ESD bleeding, delayed perforation, secondary peritoneal, or abdominal infection.

3.3. Pathological characteristics

All of the 7 specimens were pathologically diagnosed as Dieulafoy lesion. The pathological results revealed 1 or more dilated, thick mural, and tortuous arteries which were defined in submucosa or muscularis propria. These arteries had no intrinsic mural abnormality. Immunohistochemistry staining was performed and showed that CD34, CD31, and SMA were positive which supported the diagnosis of thick wall artery, while desmin, CD117, S-100, Dog-1, and Ki-67 were negative.

3.4. Follow-up outcomes

All the patients were followed up for 1 to 53 months. Gastroscopy, EUS, abdominal ultrasonography, or CT scan

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Table 1
Demographics and clinical data of the patients with silent gastric Dieulafoy lesion.

| Patients | n | %  |
|---------|---|----|
| Age (mean ± SD) | 57.7 ± 4.15 |
| Gender (n, %) |  |  |
| Male | 2 | 28.6 |
| Female | 5 | 71.4 |
| Clinical symptoms (n, %) |  |  |
| Abdominal discomfort | 3 | 42.8 |
| Abdominal distension | 2 | 28.6 |
| Epigastric pain | 1 | 14.3 |
| Acid reflux | 1 | 14.3 |
| Upper GI bleeding | 0 | 0.0 |
| Others | 0 | 0.0 |
| Distribution (n, %) |  |  |
| Antrum | 4 | 57.1 |
| Fundus | 2 | 28.6 |
| Body | 1 | 14.3 |
| Size |  |  |
| <1 cm | 1 | 14.3 |
| 1–2 cm | 6 | 85.7 |
| 2–3 cm | 0 | 0.0 |
| Layer of origin |  |  |
| Submucosa | 6 | 85.7 |
| Muscularis propria | 1 | 14.3 |
| EUS |  |  |
| Mixed echo | 3 | 42.9 |
| Hyperechogenicity | 1 | 14.3 |
| Hypoechogenicity | 3 | 42.8 |
| Complete resection | 7 | 100 |
| Complications |  |  |
| Intraoperative bleeding | 0 | 0.0 |
| Delayed bleeding | 0 | 0.0 |
| Perforation | 0 | 0.0 |
| Mortalities | 0 | 0.0 |
| Recurrence | 0 | 0.0 |

EUS = endoscopic ultrasound, GI = gastrointestinal, SD = standard deviation.
was performed on time. All the patients recovered well, and no bleeding, local recurrence, perforation, or abdominal infection was found during the follow-up period.

4. Discussion

Dieulafoy lesion was first reported by a French surgeon in 1884 and described as “Exulceratio simplex” by another French surgeon in more detail in 1898. Dieulafoy lesion was most commonly located in the stomach, especially the lesser curvature, within 6 to 10 cm of the gastroesophageal junction. These lesions may potentially cause severe, life-threatening, and recurrent GI hemorrhage. As a general consensus that the Dieulafoy lesion is “underdiagnosed rather than truly rare”, it is difficult to tell its accurate incidence in the general population. The difficulties in diagnosis and severe prognosis make it a challenge for clinicians in treatment of Dieulafoy lesions and prevention of bleeding. So far, endoscopic therapy is validated efficient in primary hemostasis of bleeding Dieulafoy lesions. Thermal therapy, regional injection, and mechanical therapy are 3 main aspects of endoscopic therapies. Some evidences suggested that endoscopic mechanical methods are more effective and successful than injection or thermal methods in hemostasis. With the advent of endoscopic technology and instruments, ESD has been a treatment with high feasibility and efficacy for gastric early cancers and submucosal tumors in recent years. However, as far as we know, there is no report for application of ESD for gastric Dieulafoy lesion when no hemorrhage occurs. In this retrospective study, a total of 7 patients with silent Dieulafoy lesion was primarily diagnosed as suspected GIST and underwent successful resection via ESD without any complications and recurrence during the follow-up. Thus, ESD treatment might be safe and effective for early resection of silent gastric Dieulafoy lesions.

Dieulafoy lesions may present as hematemesis, melena, or acute massive hemorrhage which are often recurrent; however, they tended to be with nonspecific symptoms before severe bleeding. An acceptable diagnostic criterion for Dieulafoy lesion on endoscopy was summarized as follows: active arterial spurting or micropulsatile streaming from a mucosal defect < 3 mm or through normal surrounding mucosa; visualization of protruding vessel with or without bleeding, within a minute mucosal defect or through normal surrounding mucosa; and the appearance of fresh, densely adherent clot with a narrow point of attachment to a minute mucosal defect or to normal appearing mucosa. However, it is difficult to realize gastric Dieulafoy lesions before the artery penetrates the mucosa and when no hemorrhage occurs. According to previous studies, initial endoscopy can only achieve 49% successful diagnosis, and about 6% of patients may require 3 or more endoscopic examinations to establish the diagnosis. Endoscopic ultrasound, push enteroscopy, laparoscopy, wireless capsule endoscopy, and CT also contribute to establish the diagnosis. Angiography also contributes to localize the lesion when endoscopy fails. As the conventional examination for gastric submucosal epithelial tumors, EUS can help to show the original layer, size, border of them and distinguish blood vessels from other tumors. However, the practical usefulness of EUS for the detection of Dieulafoy lesions is limited. Therefore, misdiagnosis was still common especially before the artery penetrating the mucosa. In 2005, Badwal et al. reported a gastric Dieulafoy lesion with severe upper GI bleeding which presented as a mass lesion in the stomach and diagnosed clinically and radiologically as a GIST before the operation. Then, Vats et al. provided another case of a 4 × 4 cm tumor at the lesser curvature and was clinically consistent with a GIST. During the time they sprayed the lesion with water, it bled immediately. Finally, they successfully resected the tumor which proved to be a combination of Dieulafoy lesion and GIST and stopped bleeding with 4 clips. The authors believed that this novel and unique clinical presentation underscores the ubiquitous nature of Dieulafoy lesions. All the patients in the present study presented as...
nonspecific symptoms, such as abdominal comfort, and all had the lesion completely resected. These outcomes suggested that improved examination skills and early resection of Dieulafoy lesion may reduce the life-threatening bleeding incidence and mortality.

Although endoscopic therapy can achieve initial hemostasis in almost 90% of bleeding Dieulafoy lesions, there were still nearly 10% of recurrent bleeding during the seventh day after treatment. Thus, prevention of hemorrhage seems more important in the management of Dieulafoy lesions. As a congenital disease which appears more frequently in elderly males, Dieulafoy lesions need a high degree of suspicion to be detected, especially in asymptomatic younger people with suspected lesions. In the present study, complete resection of all the 7 lesions was successfully achieved by ESD without severe complications during and after the procedures. During the operation, thermal and mechanical methods could be performed simultaneously to deal with bleeding if happened. In addition, completed resection and pathology could also be provided. However, the small number of cases is the main limit of this report. Nonetheless, this may still provide an incentive for the early management of silent gastric Dieulafoy lesions.

Consequently, ESD appears to be an effective, safe, and feasible treatment for silent gastric Dieulafoy lesion. However, more multicenter and large sample studies are necessary to further evaluate the applicability of ESD for silent gastric Dieulafoy lesion.

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