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Triple A syndrome related achalasia treated by per-oral endoscopic myotomy: Three case reports

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Abstract

BACKGROUND

Triple A syndrome is a rare autosomal recessive disease characterized by adrenocorticotropic hormone-resistant adrenal insufficiency, alacrima, and achalasia. In the last five years, per-oral endoscopic myotomy (POEM) has proved highly successful in treating primary achalasia over the long term, but its long-term performance has not been certified by achalasia related to Triple A syndrome.

CASE SUMMARY

Triple A syndrome is a rare autosomal recessive disease characterized by adrenocorticotropic hormone-resistant adrenal insufficiency, alacrima, and achalasia. In the last five years, per-oral endoscopic myotomy (POEM) has proved highly successful in treating primary achalasia over the long term, but its long-term performance has not been certified by achalasia related to Triple A syndrome.Eckardt scores and esophageal manometry improved significantly during the next 2 years after POEM; however, grade-A reflux esophagitis recurred in 66.7% of patients post 12 mo POEM procedure.

CONCLUSION

Based on these case studies. POEM is recommended as a treatment for achalasia associated with Triple A syndrome.

INTRODUCTION

Triple A (Allgrove) syndrome is a rare autosomal recessive disease first characterized by J. Allgrove in 1978 [1]. Key symptoms include adrenocorticotropic hormone-resistant adrenal insufficiency, alacrima, achalasia, and autonomic disturbance. The AAAS (achalasia, adrenocortical insufficiency, alacrimia) gene responsible for this disease is localized on chromosome 12q13 and encodes for the ALADIN (alacrima, achalasia, adrenal insufficiency, neurologic disorder) protein [2].

The primary achalasia causes dysphagia by instigating esophageal primary motor disorders in the body and lower sphincter of the esophagus. These disorders include a lack of peristalsis in esophageal body and incomplete relaxation of the lower esophageal sphincter [3]. To treat the conditions resulting from idiopathic achalasia, Inoue *et al* [4] invented the per-oral endoscopic myotomy (POEM) method which cuts the circular muscle of the lower esophageal sphincter *via* a submucosal tunnel [5]. This treatment appears to be effective at reducing achalasia in both short- [6] and long-term [7]. However, there is little evidence demonstrating the efficacy of POEM to treat achalasia related to Triple A syndrome [8], which has different pathological change that is fibrosis of inner muscular plane and neuronal nitric oxide synthase deficiency [3]. From 2017 to 2018, we treated three patients with Triple A syndrome using the POEM procedure. All three had successful operations and our routine follow-ups over the following two years suggested that all had successful, long-term therapeutic results.

CASE PRESENTATION

Chief complaints

Case 1: A 27-year-old male patient visited GI department with difficult swallowing for 5 years.

Case 2: A 19-year-old male patient was admitted to our hospital for recurrent dysphagia and occasional vomiting for 5 years.

Case 3: A 17-year-old male patient presented dysphagia with recurrent vomiting for 14 years and moderate hyper pigmentation of the skin for 6 years.

History of present illness

Case 1: From 2013, this patient had difficulty in swallowing and intermittent vomiting after meals without progressive exacerbation.His Eckardt score was 4.

Case 2: From 2012, this patient swallowed difficultly and vomitted occasionally. His Eckardt score was 4.

Case 3:From 2004, this patient presented dysphagia, recurrent vomiting and occasional chest pain. His Eckardt score was 7.

History of past illness

Case 1:As a toddler, he presented dark pigmentation around his mouth and in his skin. At 5 years old, he was diagnosed with Addison's disease and administered cortisone for substitute therapy.

Case2:At 5 years old, he was diagnosed with Addison's disease after a fever seizure comorbid with dark skin around mouth and absent tears. For this, he was prescribed cortisone treatment.

Case3:A month ago, he was diagnosed with hypoadrenalism and prescribed prednisone.

Personal and family history

Case 1:The patient had no previous or family history of similar illness.

Case 2: His brother was diagnosed with Addison's disease at 5 years old.

Case 3:The patient had no previous or family history of similar illness.

Physical examination

Case 1: This patient's temperature was 36.1℃,heart rate was 68bpm, and respiratory rate was 14 breaths/min.He was well developed (weight 50 kg,height 160 centimeters).For physical examination,no abnormalities were found.

Case2: This patient's temperature was 36.5℃,heart rate was 74bpm, and respiratory rate was 15 breaths/min.He was well developed (weight 49 kg,height 169 centimeters).He appeared alacrima while crying.

Case3:This patient's temperature was 36.5℃,heart rate was 76bpm,and respiratory rate was 25 breaths/min.He was well developed (weight 60 kg,height 185 centimeters).He presented moderate hyper pigmentation of the skin, gums, and areola.He was lack of tears while crying.

Laboratory examinations

Case 1: This patient's serum cortisol was low at 0.89ug/dL(4.0-22.3).

Case 2: This patient's serum cortisol was below 0.50ug/dL(4.0-22.3).

Case 3 :This patient's serum cortisol was 1.70ug/dL(4.0-22.3).

Imaging examinations

Case 1: This patient underwent a barium swallow which revealed the presence of typical achalasia, i.e., a mild dilated upper esophagus that tapered smoothly at its distal end into a "bird's beak" shape. Subsequently, esophageal manometry was performed which identified his condition as type II achalasia, characterized by high integrated relaxation pressure (IRP4s) (20.6 mmHg) in the lower esophageal sphincter (LES), failed peristalsis, and esophageal pressurization. He also underwent several endoscopic assessments. Esophagogastroduodenscopy (EGD) revealed esophageal dilation with fluid retention, the presence of an esophageal rosette at the esophagogastric junction (EGJ), and strong resistance when the endoscope was passing through the cardia. Endoscopic Ultrasonography (EUS) indicated no tumors but showed thickening of the

muscularis propria to 4.4 mm in the circular muscle layer and 1.4 mm in the longitudinal muscle layer.

Case 2 :This patient's barium swallow test revealed medication passing EGJ slowly, mild esophageal dilation, and a sharpening of the lower esophagus. Esophageal manometry tests showed high pressure in the LES, IRP4s (30.6 mmHg), normal UES, lack of peristalsis in the esophageal body, and esophageal pressurization. These symptoms are characteristic of achalasia type II In his endoscopic evaluations, EGD revealed a slight expansion of the esophagus, a tightly closed EGJ, and resistance when the endoscope was passed through the cardia. The EUS probe detected no tumors, but uncovered thickening of the circular muscularis propria (3.3 mm) and the longitudinal muscularis propria (0.8 mm).

Case 3: In this patient's barium swallow, the cardiac was too tight for barium to pass through, so barium reflux and multiple peristalsis waves were observed instead. These symptoms are characteristics of achalasia type I. Later, this diagnosis was confirmed with esophageal manometry, in which his distal contractile integral (DCI) was 132 mmHg.s.cm and the IRP4s in lower esophageal sphincter was 34 mmHg. On his EGD, his esophagus was mildly dilated and the cardiac was closed tightly, such that there was strong resistance to the passing of the endoscope. However, his abdominal computed tomography (CT) scan was normal.

FINAL DIAGNOSIS

Case 1:A diagnosis of Triple A syndrome was made based on the manifestation of adrenal insufficiency and achalasia (2A).

Case 2:This patient was diagnosed with Triple A syndrome based on his clinical symptoms and indication of AAAS gene mutation.

Case 3:Based on this patient's presentations, the diagnosis of Triple A syndrome was made.

TREATMENT

Informed consent was collected from all patients who were diagnosed with achalasia related to Triple-A syndromes. The patients then underwent the POEM procedure under general anesthesia in our digestive endoscopic center. A flexible, high-definition, diagnostic gastroscope with dedicated water-jet channel (GIF-HQ290) with a dissection cap was chosen.

Modifying the original POEM method of Inoue *et al* [1], our POEM procedure constituted four main steps.

Step 1 - Esophageal mucosa incision: Saline with methylene blue was first injected into submucosal layer at approximately 7 cm proximal to EGJ to lift mucosa on the posterior wall of esophagus and create an entry tunnel. A "T"-shaped incision (1 cm long, 1 cm wide) was cut using Hook knife (Hook knife, KD-620; Olympus, Corporation).

Step 2 - Submucosal tunneling: The endoscope with Hook knife was placed into the entry tunnel in the submucosal layer and used to elongate the tunnel using submucosal dissections made by short electronic cuts under Endocut mode (ERBE VIO 300D, Germany). The tunnel was extended until it reached 3 cm distal to the EGJ.

Step 3 - Selective incision of esophageal sphincter: When the cardiac sphincter was clearly exposed, myotomy was performed from the lower esophagus to the end of tunnel in both the circular and partial longitudinal layers.

Step 4 - Closure of the mucosal flaps: After completion of the myotomy, the entrance of the tunnel was closed with clips.

After receiving the POEM procedure, patients were instructed to fast for three days, during which time they were observed for mediastinal emphysema, postoperative hemorrhage, or other complications.

OUTCOME AND FOLLOW-UP

Case 1: The POEM procedure was conducted in 33 minutes with no complications. After three days, the patient could hold down food and reported relief of symptoms. Consequentially, he was discharged. Twelve months post-procedure, his IRP4s had decreased by ~18 mmHg. Consequentially, his Eckardt score dropped to 0 point and his

esophagus narrowed at its widest distance from 3.3 cm to 3.1 cm. However, as scored by the Los Angeles Classification System, Grade A (LA-A) reflux esophagitis (RE) manifested at 12 mo post-operation, and so the patient was placed on anti-acid medicine. At 24 mo post-operation, he reported no symptoms in an online consultation. His Eckardt score remained at 0.

Case 2: His POEM procedure lasted 40 minutes with no complications. Three days after his operation, he was able to consume food without dysphagia and vomiting. The patient received a follow up esophageal manometry, barium swallow, and EGD 12 and 24 mo post-procedure. His esophageal manometry showed reduction of IRP4s from baseline 30.6 mmHg to10.4 mmHg after one year and a slight increase to 12.1 mmHg after two years. New cardia relaxation degraded was also detected after 24 mo. While his Eckardt score decreased to 0 after 12 mo, it increased to 1 point after 24 mo. RE (LA-A) developed at 12 mo and was treated with proton pump inhibitors (PPI), successfully not deteriorating after 24 mo.

Case 3: The patient successfully underwent POEM, which was completed in 45 minutes. On the third day post-procedure, he was allowed to take food. He did not report difficulty in swallowing, vomiting, or chest pain. His DCI dropped to 62 mmHg.s.cm at 6 mo post-POEM from 132 mmHg.s.cm prior to the operation. At 12 mo after the procedure, he received a second esophageal manometry and EGD. RE was not detected on the EGD. Over the course of the 24-month observation period, his Eckardt score was maintaining 0 point.

DISCUSSION

While the esophageal width of these patients was only mildly wider than normal, all manifested more severe symptoms than patients with idiopathic achalasia caused by a decreased number of myenteric ganglia, lymphocytic infiltrate, and collagen deposition within the ganglia [9]. On the other hand, the main histopathologic change resulting from achalasia related to Triple A Syndrome is fibrosis of the inner muscular plane and neuronal nitric oxide synthase deficiency [10]. As a result, pneumatic dilation (PD) is not

effective over the long term with long-term efficacy decreasing to 40-50% [11,12], leading to severe fibrosis from repeated muscle tears, which is the major reason of perforation [13,14]. While two patients with achalasia related to Triple A syndrome have been treated a single time with PD and experienced symptom alleviation within a year [15], there still is little evidence confirming the efficacy of this treatment over the long term. Unlike PD, POEM was an ideal candidate for treating achalasia due to its two main theoretical advantages. First, submucosal tunnel provides endolumenal space in which endoscopists can freely adjust the length and depth of incision on the individual obstructed cardia and lower esophagus [5,6,16]. Second, it is easy to obtain a biopsy from the muscular layer during this procedure that is valuable for further treatment. Biopsying during the POEM procedure is additionally less invasive than using other methods [17]. Although we did not collect muscle biopsy for these three patients, we did obtain muscularis specimens during these procedures and have planned biopsy tests for future study.

In terms of POEM techniques, T-shape incision and Hook knife were found to be recommended. The T-shape incision combines the benefits of both longitudinal and transverse incisions, providing more flexibility to allow the endoscope to enter submucosal tunnel, and is easier to suture with clips after the operation [18]. Hook knife is more effective and usable than Dual knife. Its hook can be rotated by turning the handles to pull or push targeted fibers, thereby making dissections and incisions under Endocut mode. Lastly, the hook is practical for hemostasis for the majority of hemorrhage instead of changing Coagrasper regularly. As a consequence, we were able to complete the operation within 33-45 minutes, a significantly shorter period than the 45-174 minutes calculated by Stavros [19].

The three patients in this case study successfully had their achalasia relieved after the POEM procedure, as indicated by their sharply decreased post-operative Eckardt scores. Only in once cases did symptoms remanifest, with the patients' Eckardt score increasing to 1 point at 24th month post POEM. Overall, the patients' esophageal manometry results (IRP4s and DCI) declined largely, except again in the second case

where the patient's IRP4s slightly rebounded by 2 mmHg at the 24th month post-operation. Other research studies about treating primary achalasia suggest that 83% of patients who received POEM had no needs for reinterventions over the long-term [7,19,20]. Specifically, their overall symptoms improved substantially in the five years post-POEM, although there was mild resurgence of certain symptoms starting in the second year. The remaining 17% of patients had to receive a second operation or additional operation. These patients also appeared to have promising initial results, but developed worsening symptoms during the later phases [7,19,20]. Hence, follow-up consulting is crucial, especially for patients with Triple-A syndrome owing to lack of these rare case studies.

In terms of surgical complications, our three POEM patients did not initially feel acid regurgitation, but two patients later suffered graded LA-A reflux esophagitis by the 12th month post-POEM. They were placed on anti-secretory therapy, which resolved their symptoms. Similar studies suggest that while POEM can lead to high rate of gastroesophageal reflux (GER), the percentage of patients experiencing this complication decreases from 38% at 12 mo to 13% at 60 mo after daily treatment with PPI or histamine H2 antagonist (H2A) [6,7]. This is a key symptom which should be looked for and treated in follow-up examinations.

CONCLUSION

In summary, these three patients were successfully treated with the POEM procedure. Their main symptoms of achalasia were largely relieved even after two years post-operation. POEM may be a promising procedure as the first line treatment for Triple A syndrome related achalasia, because of its safety and efficacy.

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