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

Liu FC *et al*. Triple A syndrome-related achalasia

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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 5 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 past 5 years, 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 2 years following POEM; however, grade-A reflux esophagitis recurred in 66.7% of patients in 12 mo post-procedure.

CONCLUSION

Based on these case studies, POEM is efficacious and safe for a treatment of achalasia associated with Triple A syndrome.

**Key Words:** Per-oral endoscopic myotomy; Triple A syndrome; Achalasia; Case report

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**Core Tip:** Per-oral endoscopic myotomy (POEM) has proved an ideal way to treat primary achalasia in both short- and long-term but there is little evidence for achalasia related to Triple A syndrome, a rare disease. Herein, we enrolled three patients and performed POEM on them. During the following 2 years, we evaluated them by Eckardt score, barium swallowing test and Esophagogastroduodenoscopy. As a result, they all improved in all aspects.

**INTRODUCTION**

Triple A (Allgrove) syndrome is a rare autosomal recessive disease first characterized by Allgrove *et al*[1] in 1978. 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 the 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 changes including fibrosis of the 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 of them had successful operations and our routine follow-ups over the following 2 years showed that all of them had successful long-term therapeutic results.

**CASE PRESENTATION**

***Chief complaints***

**Case 1:** A 27-year-old male patient visited the Department of Gastroenterology who had difficulty in 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 with dysphagia and 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 had difficulty in swallowing with occasional vomiting. 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:** He presented with dark pigmentation around his mouth and in his skin when he was a toddler. At 5-years-old, he was diagnosed with Addison’s disease and administered cortisone for substitute therapy.

**Case 2:** At 5-years-old, he was diagnosed with Addison’s disease after a fever seizure comorbid with dark skin around mouth and absence of tears. For this, he was prescribed cortisone treatment.

**Case 3:** 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 68 bpm and respiratory rate was 14 breaths/min. He was well developed (weight 50 kg, height 160 centimeters). No abnormalities were found in physical examinations.

**Case 2:** This patient's temperature was 36.5℃, heart rate was 74 bpm and respiratory rate was 15 breaths/min. He was well developed (weight 49 kg, height 169 centimeters). He manifested alacrima while crying.

**Case 3:** This patient's temperature was 36.5℃, heart rate was 76 bpm 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, areola and manifested alacrima while crying.

***Laboratory examinations***

**Case 1:** This patient's serum cortisol was 0.89 µg/dL (4.0-22.3 µg/dL).

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

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

***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 4-second integrated relaxation pressure (IRP4s) (20.6 mmHg) in the lower esophageal sphincter (LES), failed peristalsis and esophageal pressurization. He also underwent several endoscopic assessments. Esophagogastroduodenoscopy (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 a 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 characteristics 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 the 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 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[4], our POEM procedure constituted four main steps.

**Step 1:** Esophageal mucosa incision: Saline with methylene blue was first injected into the submucosal layer at approximately 7 cm proximal to the EGJ to lift mucosa on the posterior wall of the 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 3 d, 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 min with no complications. After 3 d, the patient could hold down food and reported relief of symptoms. Consequentially, he was discharged. Twelve months post-procedure, his IRP4s had decreased by approximately 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, 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 (Table 1).

**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 at 12 and 24 mo post-procedure. His esophageal manometry showed reduction of IRP4s from baseline 30.6 mmHg to 10.4 mmHg after 1 year, and a slight increase to 12.1 mmHg after 2 years. New cardia relaxation degraded was also detected after 24 mo. His Eckardt score decreased to 0 point after 12 mo while it increased to 1 point after 24 mo (Table 1). RE (LA-A) developed at the 12th 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 min. On the 3rd d post-procedure, he was allowed to take food. He did not report difficulty in swallowing, vomiting, or chest pain. His DCI dropped from 132 mmHg/s/cm prior to the operation to 62 mmHg/s/cm at 6 mo post-POEM (Table 1). At 12 mo post-procedure, he received a second esophageal manometry and EGD. RE was not detected on the EGD. Over the course of the 24-mo observation period, his Eckardt score was maintained at 0 point.

**DISCUSSION**

While the esophageal width of these patients was only mildly wider than normal, they all manifested more severe symptoms than patients with idiopathic achalasia caused by a decreasing number of myenteric ganglia, lymphocytic infiltrate and collagen deposition within the ganglia[9]. On the other hand, the main histopathologic changes resulting from achalasia related to Triple A Syndrome are 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 is still little evidence confirming the efficacy of this treatment over the long term. Unlike PD, POEM is an ideal candidate for treating achalasia due to its two main theoretical advantages. First, submucosal tunnel provides endoluminal 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. Biopsy 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 recommended. The T-shape incision combines the benefits of both longitudinal and transverse incisions providing more flexibility to allow the endoscope to enter the 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 min, a significantly shorter period than the 45-174 min calculated by Stavros[19].

The three patients in this case study successfully had their achalasia relieved after the POEM procedure, as shown in Table 1. Their Eckardt scores sharply decreased post-operative. The symptoms remanifested only once, with the patients’ Eckardt score increasing to 1 point at the 24th mo post POEM. Overall, the patients’ esophageal manometry results (IRP4s and DCI) declined significantly, except again in the second case where the patient’s IRP4s slightly rebounded by 2 mmHg at the 24th mo 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 5 years post-POEM, although there was mild resurgence of certain symptoms starting in the 2nd year. The remaining 17% of patients had to receive a second operation or additional operations. 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 mo post-POEM. They were treated with anti-secretory therapy, which resolved their symptoms. Similar studies showed that while POEM can lead to a high rate of gastroesophageal reflux, the percentage of patients experiencing this complication decreased from 38% at 12 mo to 13% at 60 mo after daily treatment with proton pump inhibitors or histamine H2 antagonist[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 2 years post-operation. POEM is a promising procedure as a first line treatment for Triple A syndrome-related achalasia due to its high safety and efficacy.

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**Footnotes**

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**Table 1 Comparison of data according to pre-oral endoscopic myotomy (POEM) and post POEM**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **Case 1** | **Case 2** | | **Case 3** |
| Eckardt score |  | | | |
| Pre-operation | 4 | 4 | 7 | |
| 12 mo post-operation | 0 | 0 | 0 | |
| 24 mo post-operation | 0 | 1 | 0 | |
| IRP4s |  | | | |
| Pre-operation | 20.6 mmHg | 30.6 mmHg | 34 mmHg | |
| 12 mo post-operation | 2.8 mmHg | 10.4 mmHg | N/A | |
| 24 mo post-operation | N/A | 12.1 mmHg | N/A | |
| DCI |  | | | |
| Pre-operation | N/A | N/A | 132 mmHg/s/cm | |
| 12 mo post-operation | 1 mmHg/s/cm | 920 mmHg/s/cm | 62 mmHg/s/cm | |
| RE |  | | | |
| Pre-operation | - | - | - | |
| 12 mo post-operation | LA-A | LA-A | - | |
| 24 mo post-operation | LA-A | LA-A | - | |

DCI: Distal contractile integral; LA-A: Los Angeles Classification System, Grade A; N/A: Not applicable; IRP4s: 4-second integrated relaxation pressure; RE: Reflux esophagitis.