

83195_Auto_Edited.docx

WORD COUNT

4194

TIME SUBMITTED

15-FEB-2023 04:09PM

PAPER ID

96632044

Name of Journal: *World Journal of Clinical Cases*

Manuscript NO: 83195

Manuscript Type: MINIREVIEWS

Pathogenesis, clinical manifestations, diagnosis, and treatment progress of achalasia of cardia

Li MY *et al.* Achalasia of cardia

Ming-Yue Li, Qing-Hua Wang, Run-Peng Chen, Xiao-Fang Su, Dong-Yang Wang

Abstract

Achalasia cardia, type of esophageal dynamic disorder, is a relatively rare primary motor esophageal disease characterized by the functional loss of plexus ganglion cells in the distal esophagus and lower esophageal sphincter. Loss of function of the distal and lower esophageal sphincter ganglion cells is the main cause of achalasia cardia, and is more likely to occur in the elderly. Histological changes in the esophageal mucosa are considered pathogenic; however, studies have found that inflammation and genetic changes at the molecular level may also cause achalasia cardia, resulting in dysphagia, reflux, aspiration, retrosternal pain, and weight loss. Currently, the treatment options for achalasia focus on reducing the resting pressure of the lower esophageal sphincter, helping to empty the esophagus and relieve symptoms. Treatment measures include botulinum toxin injection, inflatable dilation, stent insertion, and surgical myotomy (open or laparoscopic). Surgical procedures are often subject to controversy owing to concerns about safety and effectiveness, particularly in older patients. Herein, we review clinical epidemiological and experimental data to determine the prevalence,

pathogenesis, clinical presentation, diagnostic criteria, and treatment options for achalasia to support its clinical management.

Key Words: Achalasia cardia; Pathogenesis; Clinical manifestations; Diagnosis; Treatment

Li MY, Wang QH, Chen RP, Su XF, Wang DY. Pathogenesis, clinical manifestations, diagnosis, and treatment progress of achalasia of cardia. *World J Clin Cases* 2023; In press

Core Tip: Achalasia is a relatively rare primary motility esophageal disorder characterized by loss of function of the plexus ganglion cells of the distal esophagus and the lower esophageal sphincter. Histological changes in the esophageal mucosa are considered pathogenic; however, studies have found that inflammation and genetic changes at the molecular level may also cause achalasia cardia, resulting in dysphagia, reflux, aspiration, retrosternal pain, and weight loss. This review article aims to conduct a comprehensive literature review and present current knowledge about achalasia.

INTRODUCTION

As a core part of the digestive system, the esophagus plays a vital role in the transportation of nutrients. The diseases of the esophagus can be classified as anatomical injuries to the organ cavity (*e.g.*, digestive or eosinophilic stenosis) or severe dysphagia in the progression of digestive tract infection (*e.g.*, severe dysphagia of neurological origin or achalasia cardia)^[1]. Esophageal achalasia is a type of esophageal dynamic disorder (EMD). It refers to esophageal outflow tract obstruction due to impaired lower esophageal sphincter (LES) relaxation and loss of esophageal peristalsis or spasmodic contraction when the esophageal body or esophagogastric junction (EGJ) is not structurally obstructed. There are primary and secondary types of achalasia^[2,3].

Achalasia cardia is characterized by the loss of functional muscle ganglion cells in the distal esophagus and LES^[4]. Although histological changes in the esophageal mucosa have long been considered part of the pathogenesis of achalasia cardia, recent studies have found that inflammation and genetic changes may also contribute to achalasia at the molecular level. Currently, achalasia is a chronic, incurable condition. Different subtypes of achalasia respond differently to drugs and surgical treatments^[5], after which some patients develop submucosal fibrosis; this may relapse and require additional treatment. In this study, we reviewed the clinical, epidemiological, and experimental data on the prevalence, pathogenesis, clinical presentation, diagnostic criteria, and treatment options for achalasia to support its clinical management.

PREVALENCE AND ETIOLOGY

Achalasia is a relatively rare disease of the esophagus, with an incidence of 2.92 per 100000 adults and 0.11 per 100000 children and a male-to-female ratio of approximately 1:1. However, recent studies have shown that the incidence of achalasia is increasing, particularly in South America, and varies among countries^[6-8]. Achalasia has a bimodal age distribution, with most patients aged between either 20-40 or 60-70 years. Studies have also shown that the incidence of this disease increases with age^[9,10]. However, there is a lack of clinical data on adult achalasia owing to the limited number of epidemiological studies on adult achalasia and the fact that most of the data are 10 years old. van Hoeij *et al*^[11] surveyed 25% of Dutch residents from 2006 to 2014 and found that the average incidence of achalasia in the Netherlands was 2.2 per 100000 people. In 2016, Tebaibia *et al*^[12] found that the average annual incidence of achalasia in Algeria increased from 0.04 [95% confidence interval (CI): 0.028-0.052] in the 1990s to 0.27/105 inhabitants per year in the 2000s (95%CI: 0.215-0.321), and the incidence was 2.5 times higher in the north and center than in the south of the country. Thus, additional research is required to gain a better understanding of achalasia in adults.

A recent large cohort study based on the IBM MarketScan Commercial Claims and Encounters database of the United States Medicare data showed that the median age of

patients with achalasia was 52.70 years, and 56% of patients with achalasia cardia were female^[13]. According to a recent large multi-center database study conducted in Japan, male sex and family history may be risk factors for achalasia^[14]. One study found that socioeconomic status and lifestyle factors were associated with achalasia, in addition to the highest risk of developing achalasia in individuals with low-level occupations (OR = 1.88, 95%CI: 1.02-3.45)^[15]. Foreign travel history and the presence of pets in the household also increased the risk of achalasia^[16].

PATHOGENESIS OF ACHALASIA

Currently, the etiology and pathogenesis of achalasia cardia remain unclear; however, it is generally believed that the histological changes of the esophageal mucosa caused by the loss of esophageal nerve cell function play a key role in its pathophysiology. Autoimmune attack of esophageal myenteric nerves through cell-mediated and possibly antibody-mediated mechanisms may lead to the inhibition of esophageal smooth muscles, resulting in loss of nerve function and nerve fiber degeneration^[2,16].

In addition, several pathological mechanisms have been proposed as possible triggers for this immune disruption process, including underlying viral infections, idiopathic autoimmune triggers, and genetic predisposition^[17,18]. Enteric herpes zoster virus, herpes simplex virus, measles, and human papillomavirus can impair the regulation of functional esophageal movement and LES control in patients with achalasia, but not in all patients with viral infections^[19]. According to a case-control study by Naik *et al*^[20], 80% of patients with achalasia had varicella-zoster virus DNA present in their saliva. A small amount of data suggests that eosinophils and mast cells may play a role in the development of achalasia and esophageal obstructive motility disorders. The aggregation of eosinophils and mast cells in the esophagus causes an increased concentration of inflammatory cytokines; this leads to fibrosis remodeling of the esophageal wall, ultimately causing esophageal dysfunction and related symptoms^[21,22]. In 2013, Cools-Lartigue *et al*^[23] enrolled 96 patients with achalasia who underwent laparoscopic Heller myotomy (LHM) and found that many patients with achalasia had

esophageal eosinophilic infiltration. However, other studies have not found a cause-effect relationship between eosinophils and achalasia^[24].

Sara *et al*^[25] found a two-fold increase in the prevalence of autoimmune diseases in patients with achalasia cardia, which is often associated with type I diabetes (47.80%) and thyroid diseases (19.60%). In addition, patients with Sjogren's syndrome, psoriasis, autoimmune uveitis, rheumatoid arthritis, and Crohn's disease are more prone to achalasia. In addition, autoantibodies against sarcomeres are present in serum samples from patients with achalasia cardia, particularly in carriers of the HLA DQA1*0103 and DQB1*0603 alleles^[16]. Of the comorbidities identified in this study, thyroid disease and Down syndrome were the most common autoimmune and hereditary conditions, respectively. Familial achalasia, achalasia with hereditary disease, and achalasia with autoimmune disease were present in 0.63%, 0.99%, and 2.40% of cases, respectively^[14].

CLASSIFICATION OF ACHALASIA

Achalasia can be divided into three subtypes according to the Chicago classification criteria: type I achalasia accounts for 20%-40% of cases; type II achalasia, the most common, accounts for 50%-70% of cases and has the highest levels of interleukin 4; type III achalasia, the rarest and most difficult to treat, accounts for 10% of cases^[26] (Table 1). Compared with types II and III, type I is associated with lower concentrations of regulatory cells, pro-inflammatory cytokines, extracellular matrix converting proteins, and Fas receptors and higher levels of transforming growth factor- β ^[7]. Achalasia can progress from one type to another; this mainly relates to the pathological transition from ganglion inflammation to fibrosis^[27,28].

Pseudoachalasia, also known as secondary achalasia, refers to the esophageal motility disorder caused by dysphagia and weight loss due to gastric cardia tumors or infiltrating intestinal plexus tumors (gastroesophageal junction adenocarcinoma, pancreatic cancer, breast cancer, lung cancer, or hepatocellular carcinoma)^[29]. Pseudoachalasia is characterized by symptoms as well as manometry, endoscopy, and barium swallow findings similar to those of achalasia. This condition is often caused by

tumors^[30]. Moreover, in esophageal manometry, pseudoachalasia exhibits a lower incidence of complete peristalsis loss, combined relaxation pressure, and EGJ systolic scores compared with those observed in primary achalasia. Furthermore, invasive malignancies can be rapidly assessed using endoscopy and endoscopic ultrasonography or cross-sectional imaging^[7,31].

Notably, in addition to the Chicago classification for esophageal achalasia - regarded as the international standard - there is also a Japanese classification system for this condition. In addition, three endoscopic structures have been identified based on the Ling classification, including polycyclic, crescent, and diverticular structures. The new Japanese Classification system for esophageal achalasia aims for a more practical classification based on clinicopathology, and cases are divided into three types based on their X-ray results: Straight (St), S-shaped (Sg), and advanced sigmoid (aSg)^[32]. However, this system has not been widely used in Japan and has not been fully validated in terms of its demographic significance and ability to predict postoperative outcomes. The Ling classification system is a new type of endoscopic classification of achalasia cardia used to select patients who are suitable for transoral endoscopic myotomy [peroral endoscopic myotomy (POEM)] (Table 2). According to the Ling classification criteria, there are three types: Type I, smooth and without polycyclic, crescentic, or diverticular structures; type II, with polycyclic or crescent structures; and type III, with diverticular structures. Type II has three subtypes: Ling IIa, Ling IIb, and Ling IIc. Type III also has three subtypes: Ling IIIi, Ling IIIr, and Ling IIIr^[33].

CLINICAL PRESENTATION OF ACHALASIA

Dysphagia (solid or liquid) is a common symptom in patients with achalasia. This symptom is initially intermittent; however, as the disease advances, it progresses along with significant dilation of the esophagus, leading to burns and decompensation of the sigmoid esophagus with corresponding clinical symptoms^[34]. Notably, approximately 90% of people with achalasia experience the main symptoms of progressive difficulty in swallowing liquids and solids^[30].

Studies have shown that 70% of patients also experience reflux, which is the second most common symptom of achalasia; in turn, this causes corresponding respiratory symptoms such as coughing and burping, wheezing, hoarseness, and bronchitis^[35,36].

In addition, patients with achalasia may experience chest pain^[5]. There is also a risk of long-term aspiration pneumonia and esophageal squamous cell carcinoma^[17]. A study conducted using data from a United Kingdom hospital and primary care database found that patients with achalasia had a high incidence of, and mortality from, esophageal cancer, aspiration pneumonia, and lower respiratory tract infections^[37]. In addition, other studies have found that patients with achalasia have acute respiratory failure and hemodynamic instability. End-stage achalasia with thoraco-esophageal enlargement may manifest as an acute disease^[38].

Studies have found that achalasia often has an insidious onset with many subclinical features before definitive diagnosis, which can lead to a delay between symptom onset and diagnosis^[31,38]. The Eckardt score can be used to assess the symptoms of achalasia (Table 3). This is a standardized and verified scoring system that rates four symptoms of achalasia (dysphagia, reflux, chest pain, and weight loss) based on severity, each on a scale of 0 to 3 on a final 12-point scale, where higher scores indicate more severe symptoms. A score < 3 is used to define symptom remission or successful remission^[39]. Studies have shown that an Eckardt score ≥ 9 before treatment can predict the success of endoscopic myotomy in patients with achalasia cardia^[40]. There is also evidence that genetic susceptibility, environmental triggers, and autoimmune enteromyelitis determine clinical phenotypes^[41].

DIAGNOSIS OF ACHALASIA

Currently, achalasia cardia is mainly diagnosed using high-resolution manometry (HRM), endoscopy, and barium meal examination^[42]. A timed barium meal esophagogram or functional lumen imaging probe (FLIP) is used only when achalasia cannot be diagnosed^[43].

HRM

Manometry plays an important role in the differential diagnosis of dynamic esophageal disorders. HRM is the gold standard for diagnosing achalasia cardia. HRM usually refers to performing a manometry test with at least 21 pressure sensors scattered across the catheter. Each pressure sensor is spaced 1 cm apart to record baseline resting measurements. The probe enters from the nose and passes through the esophagus to the LES, allowing for the examination of the entire esophagus^[3,34,44].

The essential condition for HRM diagnosis of achalasia cardia is a comprehensive relaxation pressure (IRP) > 15 mmHg, which is defined as "impaired LES relaxation". A resting pressure > 45 mmHg is defined as a high-pressure LES^[45,46]. The IRP is the most important parameter for the assessment of LES relaxation using HRM, which is measured after the relaxation of the EGJ in anticipation of the arrival of peristaltic waves after upper sphincter relaxation^[45]. Clinical studies have shown that when LES-IRP is > 10 mmHg after treatment, repeated treatment is required^[47].

In fact, HRM may not only confirm the diagnosis of achalasia but also identify specific subtypes that have significantly different treatment outcomes^[39]. An appropriate intraoperative HRM diagnosis can help determine therapeutic approaches and predict therapeutic outcomes^[42].

Endoscopy

Endoscopy is crucial for patients with digestive disorders although it is not very sensitive for achalasia. Studies have shown that only one-third of patients can be diagnosed with achalasia using endoscopy^[48]. Typically, endoscopy is used to screen patients with gastrointestinal symptoms and to rule out luminal malignancies in the esophagus and proximal stomach^[49]. Endoscopy may be normal in patients with early achalasia as curvatures or rose-like structures at the EGJ are characteristic of patients with more advanced achalasia. In addition, Gomi *et al*^[50] found that the Champagne glass sign displayed by the endoscope could indicate achalasia. Notably, in 2020, Hoshikawa *et al*^[51] found that all patients with achalasia with "esophageal rota" had the

“ginkgo leaf sign.” This is a new finding regarding the diagnosis of achalasia. Therefore, further research is needed to confirm its sensitivity, specificity, and interobserver consistency.

Barium meal esophagogram

Barium contrast is usually used to evaluate esophageal morphology before surgery. In patients with achalasia cardia, barium meal esophagogram reveals esophageal dilation, EGJ stenosis, beak formation, intestinal peristalsis, and delayed barium emptiness^[5] (Figure 1). Studies have shown that four stages of achalasia cardia can be distinguished according to the maximum barium diameter and shape in the esophagus (Table 4): Stage 1, ≤ 4 cm; stage 2, 4-6 cm; stage 3, ≥ 6 cm, with a straight esophagus; stage 4, ≥ 6 cm, with a sigmoid tube (end-stage disease)^[5,48].

Timed barium ingestion (TBS) refers to the acquisition of static images of the esophagus at predetermined time intervals after the ingestion of a fixed amount of barium sulfate. It is an improved esophagography technique that can assess esophageal emptying more objectively^[52]. TBS can be used to evaluate treatment success. It is simple, economical, non-invasive, repeatable, and well-tolerated by patients^[45]. Notably, TBS is widely used for the preliminary evaluation of patients with suspected type I, II, or III achalasia.

FLIP

FLIP is a novel catheter-based device that can be used to analyze the relationship between cross-sectional area and pressure of the lumen, measure the EGJ and dilatation index (DI) in real time, and provide supplementary information for HRM of EMDs, especially for achalasia cardia. FLIP has become a potential tool for the diagnosis and real-time calibration of achalasia cardia^[53,54]. This device is generally suitable for patients with suspected achalasia but normal combined relaxation pressure, non-diagnostic HRM results, and those who cannot tolerate HRM testing^[55]. Ren *et al*^[56] and Carlson *et al*^[57] found that FLIP could detect esophageal contractility in patients with

achalasia that was not observed using manometry. In addition, FLIP can accurately predict the immediate outcome of balloon dilation and be used to guide the selection of balloon size for a single endoscopic balloon dilation.

Other investigations

Studies have shown that chest computed tomography (CT), radiography, and ultrasound can also detect achalasia cardia^[58,59]. Imaging is often used in the diagnosis of achalasia. Most patients with achalasia have esophageal dilation and mild symmetrical wall thickening on CT. Additionally, chest CT can be used to distinguish between primary and secondary achalasia cardia. Distal esophageal wall thickening (nodular/Lobular and asymmetrical); soft tissue masses at the gastroesophageal junction; mediastinal lymph node enlargement; and lung, liver, or bone metastases are suggestive of secondary achalasia^[60]. Currently, imaging is mainly used for auxiliary examinations.

TREATMENT OF ACHALASIA

Treatment of achalasia cardia involves drugs, endoscopic Botox injections, and surgery to reduce LES pressure, relieve the patient's symptoms, and improve esophageal emptying; however, the condition cannot be cured. Surgical treatment for this disease is controversial as the related procedures may lead to gastroesophageal reflux; moreover, each treatment has particular limitations.

Medication

Medication is usually adopted in ³ patients who cannot, or refuse to, undergo endoscopic or surgical treatment and in those for whom endoscopic or surgical treatment has failed (Table 5). Calcium channel blockers, nitrates, and proton pump inhibitors are commonly used to control acid reflux; however, they provide only short-term relief and are less effective^[49].

Endoscopic treatment

Traditional endoscopic treatment of achalasia involves injections of botulinum toxin type A, pneumatic dilation (PD), and sclerotherapy.

Botulinum toxin type A: Botulinum toxin type A originated in 1980. It is a biological neurotoxin released by *Clostridium botulinum* that can prevent the release of acetylcholine from voluntary and involuntary muscle nerve endings^[61]. It is considered an effective treatment for short-term symptomatic relief in patients with esophageal achalasia. This treatment is initially effective, but the outcome of repeated usage is poor, and the maintenance time is short (approximately 6-9 mo). Yamaguchi *et al*^[61] found a high degree of remission of dysphagia after 1 wk of botulinum toxin treatment; however, 50% of patients relapsed 3-24 mo after treatment.

PD: Originating in 1674, PD is the earliest form of treatment for types I and II achalasia cardia. This method involves the use of an inflated balloon with a strong stretch to destroy the LES. The diameter of the balloon can range from 30 to 40 mm. Although short-term results of PD are adequate, the long-term outcomes are poor, requiring multiple treatments^[39]. The most commonly used expander is the Rigiflex, which is usually ≥ 3 cm in diameter when fully inflated^[62,63]. However, the effectiveness of the treatment decreases over time, and repeated treatment is required. A multicenter randomized controlled trial that compared aerated dilation with LHM indicated that 25% of patients with achalasia who received PD required retreatment^[64]. Similarly, Jung *et al*^[65] conducted a 1-year follow-up study of 73 Korean patients with achalasia cardia and found that balloon dilation was more effective than botulinum toxin in providing long-term relief.

Endoscopic sclerotherapy: Currently, the commonly used hardener ethanolamine oleate can induce an inflammatory response and fibrosis, thus causing excitatory neuronal damage and reducing LES pressure^[66]. However, this method can cause

patients to develop esophageal wall fibrosis; therefore, it is not recommended for routine use^[7].

Operative treatment

Surgical treatments for achalasia include POEM, LHM, stent implantation, and esophagectomy (Table 6).

LHM: LHM is a common clinical treatment for achalasia, especially in adolescents and young adults, with a success rate of approximately 90%; however, the adverse outcome of gastroesophageal reflux disease (GERD) can occur in 55%-100% of cases. Subsequently, to compensate for the damage caused by esophageal reflux disease, LHM combined with anterior Dor fundoplication or posterior Toupet fundoplication was introduced^[42,47,67]. Access to acid-lowering medication is required, and trauma, scars, and complications of esophageal or gastric perforation may occur^[62]. Studies have shown that robot-assisted Heller myotomy (RAHM) is safer than LHM and can significantly reduce the incidence of esophageal perforation^[63]. A recent review suggested that RAHM is safe and effective for the treatment of achalasia cardia and for that of esophageal dyskinesia, owing to its low incidence of technical complications compared to that for LHM^[68].

POEM: Recently, POEM has emerged as an alternative to LHM. Introduced in 2008, this technique is a new minimally invasive therapeutic endoscopic surgical technique that is especially suitable for patients with type III achalasia cardia^[47]. This operation involves establishing a submucosal tunnel in the lower esophagus to reach the LES' inner ring muscle bundle for myotomy while preserving the external longitudinal muscle bundle; this can prevent body wall trauma and preserve the external esophageal anatomy, while being precise and minimally invasive^[46,62]. One advantage of POEM over LHM is that it can adjust the proximal myotomy range^[69]. A recent study reported a 19-fold increase in the use of POEM. In addition, POEM can be used to perform a real-time

direct biopsy of muscle layers and easily control the length and location of the myotomy^[70]. Wang *et al*^[71] conducted a multicenter, randomized controlled trial to follow-up patients with type II achalasia who underwent POEM and PD for 5 years and found that transoral endoscopic myotomy was superior to PD, with fewer complications, and should be recommended as the initial treatment option for patients with achalasia cardia. In addition, a meta-analysis indicated that the 2-year success rate of POEM treatment was significantly improved compared with that of inflatable dilation in first-time patients; however, reflux esophagitis was more common in the POEM group than in the inflatable dilation group^[72].

A study comparing POEM with LHM found that POEM was safer and even superior to LHM in terms of cost-effectiveness, length of hospital stay, and dysphagia relief^[28,46]. One study showed an early success rate of 89%-100% for POEM and that it is highly effective in the management of type III achalasia cardia^[73]. Schlottmann *et al*^[35] conducted a meta-analysis of 2000 cases of POEM reported in 21 articles worldwide and found that POEM is a relatively safe procedure with low morbidity and mortality rates.

Studies have shown that the POEM technique has certain drawbacks that can lead to GERD because POEM is not combined with anti-reflux surgery^[39]. One study indicated that 41% of patients developed reflux esophagitis after POEM^[74]. Similarly, a 2-year follow-up study showed that POEM was not inferior to LHM combined with Dor fundoplication in controlling the symptoms of 2-year achalasia cardia; however, compared with LHM patients, POEM patients were more prone to GERD. Nabi *et al*^[75] found that GERD is very common after POEM; moreover, Barrett's esophagus - a potential long-term sequela of postoperative reflux - may also occur if the reflux persists long term. In addition, studies have shown that although POEM is a promising new therapy, most endoscopists worldwide have not yet mastered this technique owing to its high technical requirements and steep learning curve. POEM can also be challenging^[63].

It is important to note that long-term follow-up is necessary for patients with achalasia cardia who undergo POEM, which can be used to monitor clinical,

radiological, and manometry therapy success; functional changes in GEJ; and pathological gastroesophageal reflux. The follow-up duration is usually 3-6 mo after discharge. The Eckardt score should be assessed, and endoscopy, manometry, and timed barium meal examinations should be performed. If necessary, esophageal dilation and a 24-h esophageal pH test may be performed^[76].

Stent implantation: Self-expanding metal stents (SEMS) have long been used in the management of both benign and malignant diseases of the esophagus. Esophageal stent implantation is a technique that slowly expands the stent to a predetermined diameter, breaks the LES muscle fibers, and reshapes them to reduce LES pressure. Currently, temporary SEMS are mostly used for treatment^[77].

Stenting therapy has been effective in nearly 100% of patients with achalasia for more than 8 years^[78]. Stents are considered a safe and effective treatment because of their uniform dilating tension; however, they do not provide sustained symptom relief and are prone to complications, such as stent displacement, regurgitation, perforation, bleeding, and, most importantly, stent-induced tissue proliferation leading to new stenosis^[27,78,79]. Currently, a biodegradable scaffold exists that can be used in the elderly; however, its efficacy requires further investigation.

Esophagectomy: Owing to the development of endoscopic technology and the maturity of minimally invasive surgical operations, esophagectomy has rarely been used. Patients with surgical failure and end-stage achalasia cardia can undergo esophagectomy. In 2018, the International Society for Esophageal Diseases guidelines recommended esophagectomy for patients with persistent or recurrent achalasia after minor invasive treatment failure and disease progression^[7].

CONCLUSION

Achalasia is a relatively rare disease of esophageal motility. Its main clinical manifestations are dysphagia, reflux, chest pain, and weight loss; these may

significantly reduce a patient's quality of life. The treatment of achalasia cardia mainly aims to relieve symptoms since the disease is incurable. POEM is expected to become the optimal means of treating achalasia cardia owing to its effectiveness and safety. Personalized treatment should be provided according to the clinical characteristics of each patient. Currently, clinical research on achalasia cardia suggests the possibility of infectious events related to certain genetic factors that trigger the autoimmune mechanism. However, further research is necessary in the related fields to explore optimal treatment plans.

6%

SIMILARITY INDEX

PRIMARY SOURCES

1	www.researchgate.net Internet	48 words — 1%
2	www.wjgnet.com Internet	36 words — 1%
3	www.ncbi.nlm.nih.gov Internet	32 words — 1%
4	www.science.gov Internet	28 words — 1%
5	link.springer.com Internet	27 words — 1%
6	Ryo Kato, Kiyokazu Nakajima, Tsuyoshi Takahashi, Koji Tanaka et al. "Validation of new Japanese classification system for esophageal achalasia", Esophagus, 2019 Crossref	16 words — < 1%
7	www.f6publishing.com Internet	14 words — < 1%
8	www.nature.com Internet	14 words — < 1%

-
- 9 G Zaninotto, C Bennett, G Boeckxstaens, M Costantini et al. "The 2018 ISDE achalasia guidelines", Diseases of the Esophagus, 2018
Crossref 13 words — < 1%
-
- 10 Cassarano Sara, Pesce Marcella, Cargioli Martina, Andreozzi Marta et al. "Clinical correlation and disease phenotype in patients with esophageal achalasia and comorbid autoimmune diseases", Diseases of the Esophagus, 2020
Crossref 12 words — < 1%
-
- 11 Alberto Pietrantoni, Simona Seriola, Manuela Cominelli, Giovanni Lodoli et al. " Lactotroph /adenoma associated to granulomatous hypophysitis in a patient with Crohn's disease: A case report ", Neuropathology, 2022
Crossref 10 words — < 1%
-
- 12 escholarship.umassmed.edu
Internet 10 words — < 1%
-
- 13 jeccr.biomedcentral.com
Internet 10 words — < 1%
-

EXCLUDE QUOTES ON

EXCLUDE SOURCES < 10 WORDS

EXCLUDE BIBLIOGRAPHY ON

EXCLUDE MATCHES < 10 WORDS