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А.Ю. Ищенко*, М.Ю. Галушко

Медицинский центр «МедЭлит», ООО «МедЭлитКонсалтинг», Москва, Россия

ГАСТРОЭЗОФАГЕАЛЬНАЯ РЕФЛЮКСНАЯ БОЛЕЗНЬ С РАЗВИТИЕМ ВТОРИЧНОГО ДИФФУЗНОГО ЭЗОФАГОСПАЗМА

A.Yu. Ishchenko*, M.Yu. Galushko

Medical center «MedElit», LLC «MedElitConsulting», Moscow, Russia

Case of Gastroesophageal Reflux Disease Resulted in Secondary Esophageal Spasm

Резюме

Гастроэзофагеальная рефлюксная болезнь — это широко распространённое хроническое заболевание, характеризующееся забросом в пищевод желудочного или дуоденального содержимого. Эзофагоспазм и ахалазия кардии являются недостаточно изученными заболеваниями, связанными с нарушением нервно-мышечной передачи импульса и дискоординацией моторики пищевода, проявляющимися загрудинной болью и дисфагией. В статье представлен клинический случай молодого пациента с гастроэзофагеальной рефлюксной болезнью и анамнезом нетипичных загрудинных болей, требующих дифференциального диагноза между вариантами нарушенной моторики пищевода.

Ключевые слова: гастроэзофагеальный рефлюкс, эзофагит, эзофагоспазм, ахалазия кардии

Конфликт интересов

Авторы заявляют, что данная работа, её тема, предмет и содержание не затрагивают конкурирующих интересов

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Abstract

Gastroesophageal reflux disease is a widespread chronic disease in which stomach or duodenal contents rise up into the esophagus. Esophageal spasm and achalasia cardia are poorly studied disorders associated with impaired neuromuscular impulse transmission and motor discoordination of the esophagus, manifested by chest pain and dysphagia. The article presents a clinical case of a young patient with gastroesophageal reflux disease and a history of atypical chest pain requiring differential diagnosis between variants of impaired esophageal motility.

Key words: gastroesophageal reflux, esophagitis, esophageal spasm, achalasia cardia

Conflict of interests

The authors declare no conflict of interests

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ORCID ID: https://orcid.org/0000-0002-0730-3800

^{*}Контакты: Алина Юрьевна Ищенко, e-mail: iecurmed@yandex.ru

^{*}Contacts: Alina Yu. Ishchenko, e-mail: iecurmed@yandex.ru

 $\label{eq:GERD-gastroesophageal reflux disease, DES-diffusive esophagism, PPIs-proton pump inhibitors, MAFLD-matabolism-associated fatty liver disease, NAFLD-non-alcoholic fatty liver disease, LES-lower esophageal sphincter, RS-radiographic contrast study, UDCA-ursodeoxycholic acid, EGDS-esophagogastroduodenoscopy, DCI-distal contractile integral, IRP-integrated relaxation pressure$

Gastroesophageal reflux disease (GERD) is a chronic recurrent disease caused by impaired motor-evacuation function of gastroesophageal organs and characterised by recurrent reflux of gastric and sometimes duodenal contents into the esophagus. In Russia, the incidence of GERD in adults varies from 11.3 to 23.6% [1]. GERD-associated factors are the age of over 50 years and smoking, and the main comorbidity is obesity. A typical set of symptoms includes hearburn, belch, regurgitation, odynophagia. Symptoms worsen in prone position and when by bending over.

Esophagism is a gastric disease caused by spastic contraction of the gastric wall without cardia opening disorders following a gulp [2]. Esophagism pathogenesis in unknown; it is assumed that the disorder is caused by defective neurotransmission. Russian and foreign literature sources have no references to any clinical, laboratory, and instrumental signs of esophagism which can reliably confirm or invalidate the diagnosis. Depending on the causes, esophagism can be primary (caused by organic changes in the nervous system) and secondary (caused by GERD, gastroesophageal hernia, esophagitis); in terms of the involvement pattern — segmental or diffusive (DES) [2].

Esophageal achalasia (idiopathic esophageal dilatation, cardiospasm) is an idiopathic neuromuscular disease, manifestations of which include functional disorders of cardia patency due to incoordination between gulping, reflex opening of the lower esophageal sphincter (LES), and motor and tonic activity of smooth gastric muscles [3]. The main symptoms of the disease are progressive dysphagia, regurgitation and retrosternal pain caused by incomplete esophagus evacuation and chronic esophagitis.

Case Study

Patient D., 33 years old at first visit in October 2019. **Complaints:** Pain in xiphoid appendix area, especially in prone position and when the patient eats crude vegetable fibers (hard apples, cabbage, beetroot) and drinks water. The pain worsens during speaking.

Medical history:

 According to the patient, the onset of the disease was in 2013 (when he was 27 years old), when the above complaints appeared for the first time. At that time the patient had his first esophagogastroduodenoscopy (EGDS), and reflux esophagitis was diagnosed. He had several courses of proton pump inhibitor (PPI) therapy (various doses and regimens of omeprazole, rabeprazole, esomeprazole) and promotility agents (domperidone, itoprid, trimebutine, various duration) without any marked effect. At the same time, the patient followed all non-drug recommendations for GERD patients.

- In 2016, the patient underwent a 24-hour pH monitoring and gastric manometry; all results were normal. Also, he had cardia dilatation without any clinical effect. The patient denied dysphagia and regurgitation both before and after dilatation.
- Over the period from 2016 to 2018, several examinations recommended by cardiologist and neurologist did not resolve the pain the patient suffered from.
- In 2018, when there was no effect from conservative therapy, the patient was recommended to undergo gullet bougienage, but he refused because of possible complications.
- Before visiting MedElite Medical Center (MedElite-Pro LLC) in October 2019, the patient took PPIs and promotility agents from time to time without prescription and without any clinical effect; he underwent several esophagogastroduodenoscopy (EGDS) procedures, that revealed cardia insufficiency; peptic esophagitis; esophagus erosions and superficial gastritis (twice); duodenogastric reflux (from time to time).
- In February 2019, the patient underwent first-line eradicative anti-helicobacter therapy without any clinical changes during and after therapy.

Life history: Occasional smoking up to 2009 (4 years before complaints appeared), alcohol consumption — non-toxic doses no more than three times a year. No allergic background. In 2012, the patient had antiviral therapy for chronic hepatitis C with direct-acting antiviral drugs, and sustained virological response was achieved; hepatic fibrosis stage F0 as demonstrated by transient elastometry (2017). Familial history: his mother has type 2 diabetes mellitus, chronic thyroid gland disorder.

Physical examination: Satisfactory condition. The patient is emotionally stable, cooperative, has regular normosthenic constitution with moderately developed subcutaneous fat and muscles; BMI: 25.2 kg/m², abdominal circumference: 90 cm. The skin has physiological shade and is moderately moist; hand skin is dry.

The oral cavity is restored to health; the tongue is moist, with white coat Respiratory system: the chest is symmetric and is evenly engaged in respiration; no abnormalities by palpation; clear pulmonary tones by percussion; auscultatory vesicular respiration in all chest sections; without stridor. Cardiovascular system: regular cardiac rhythm; clear heart tones without any murmur or diastolic shock; heart rate (HR) is 72 bpm, blood pressure (BP) is 122/77 mm HG on both arms. Abdomen: evenly engaged in respiration; soft, painless. The liver is within the costal arch and is not enlarged by percussion. Cholecystic symptoms are negative. Peritoneal signs are negative. Kidney punch is negative on both sides. Peripheral oedema is not observed. Bowel and bladder habits are normal.

Preliminary diagnosis: gastroesophageal reflux disease — endoesophagitis, a history of erosive esophagitis. A history of duodenogastric reflux. H.pyloriassociated chronic superficial gastritis, condition after first-line eradicative therapy (February 2019). Esophageal achalasia?

Examination results:

- Complete blood count and blood chemistry: unremarkable.
- EGDS revealed cardia insufficiency, peptic esophagitis (biopsy was performed in order to exclude Barrett's esophagus, and the histology report demonstrated the presence of esophagitis without any signs of metaplasia), superficial gastritis, duodenitis, duodenogastric bile reflux; rapid urease test for H.pylori came positive, pH 7 (Fig. 1).
- Abdomen US examination revealed focal masses in right lobe of liver with signs of haemangiomas and regular echo structure in remaining liver parenchymatous tissue with even contours. Also, the

- examination revealed deformed gall bladder without signs of cholestasis and biliary hypertension, with signs of pancreatic lipomatosis. No sonographic signs of portal hypertension and changes in spleen.
- High-resolution gastric manometry showed resting pressure in lower esophageal sphincter (LES) of 10–12 mm Hg (normal value: 10–45 mm Hg). No hiatal hernia was found. Diagnosis according to The Chicago Classification of Esophageal Motility Disorders, v. 3 (2015): Inefficient esophageal motility: esophagogastric junction is unobstructed; IRP (integrated relaxation pressure) is < 15 mm Hg; over 50% of contractions are inefficient; DCI (distal contractile integral) is < 450 mm Hg x cm (Fig. 2).
- Barium esophagography revealed signs of gastroesophageal reflux, cardia insufficiency, peptic esophagitis, duodenogastric reflux.
- 24-hour esophagus pH-impedancemetry at the level of 5 cm above LES revealed 7 acidic refluxes (normal value: < 50) with the total duration of 8 min (normal value: < 60). Acidic refluxes, vertical position (daytime): 7, horizontal position (during sleep): 0. Chemical clearance lasted for 1 minute (normal value: < 3 minutes). Duration of pH < 4.0 episodes during the day was 0.6% (normal value: < 4.5 %). De Meester score was 2.19 (normal value: < 14.72). Impedancemetry signal analysis results: low acidity refluxes during the day was 20 (normal value: < 21), alkaline refluxes during the day was 32 (normally, they should be absent). At the same time, over 60 % of the time, gastric pH was over 4.0, therefore, hypoacidic gastritis was suspected; signs of duodenogastric reflux were recorded from 6.00 am to 8.00 am (Fig. 3).

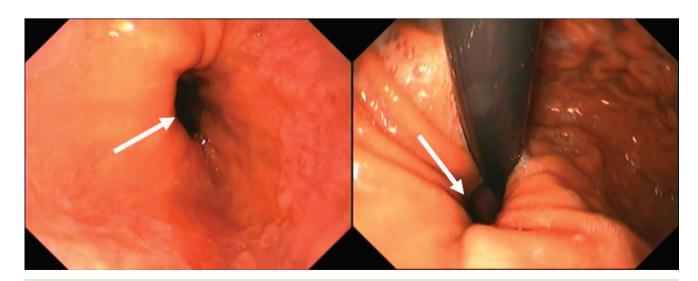
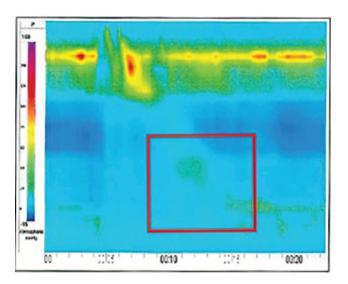


Figure 1. Cardiac sphincter on endoscopy: insufficiency on direct and retroversion examination (marked with white arrows).



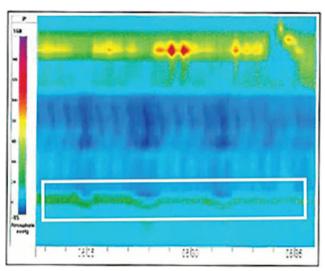


Figure 2. Esophageal manometry. The red frame highlights the absence of esophageal contraction in swallow phase; DCI is 31 mm Hg, with the normal range of 450-8000 mm Hg. The white frame highlights the LES pressure at rest, equal to 12 mm Hg with the normal range of 10-45 mm Hg.

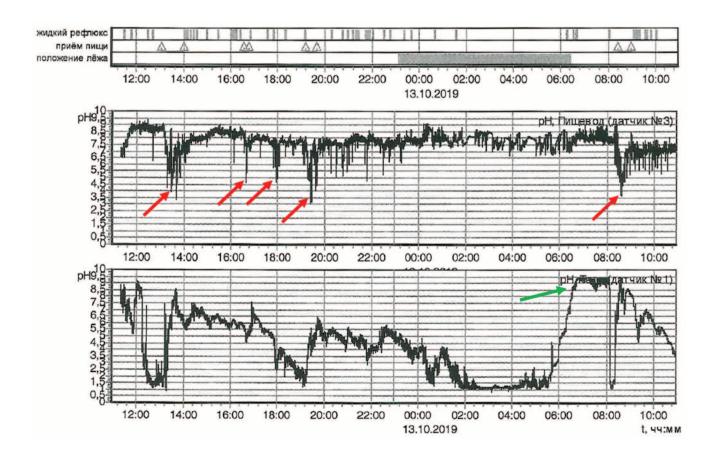


Figure 3. The result of 24-hours pH-impedancemetry. The red arrows indicate acid refluxes into the esophagus. The green arrow indicates alkaline duodeno-gastric reflux

Based on the results, the following diagnosis was made: gastroesophageal reflux disease — endoesophagitis, a history of erosive esophagitis. Duodenogastric reflux. Secondary diffusive esophagism. H.pylori-associated chronic superficial gastritis. Condition after eradicative therapy — first-line A and first-line B, both were ineffective. Hepatic haemangiomas.

Recommended therapy: Calcium channel blockers nifedipine with gradual dose titration to 10 mg 3 times per day — continuously; esophagus protective agent (sodium hyaluronate + chondroitin sodium sulfate), 1 sachet 3 times per day; PPI and ursodeoxycholic acid (UDCA), standard regimen — 1 month.

One and a half month after nifedipine therapy initiation, the patient noted reduction in pain intensity. With regular drug administration his condition remained stable; from time to time the patient had dull pain which did not affect the quality of his life. Five months later, the patient discontinued nifedipine (since the drug was not available on the market), and his condition deteriorated significantly in just two weeks: intense pain resumed and the patient started coughing. The patient was examined by a GP and underwent chest X-ray, the results of which excluded respiratory disorders. Nifedipine therapy resumption with titration to previous doses (30 mg daily) resulted in gradual improvement in the patient's condition over a month: cough resolved quickly, pain became less frequent and less intense. As of March 2022, the patient has been taking nifedipine regularly, 1 sachet of esophagus protective agent 1-3 times per day (in courses), PPI — standard regime (Rabeprazole 10 mg or Dexlansoprazole 30 mg once daily for 2-4 weeks). The patient undergoes annual follow-up endoscopy and histological examination, that demonstrate endoesophagitis without any negative trend. In March 2022, overweight was diagnosed: the patient gained 5 kg over 3 years (BMI: 26.9 kg/m2), his abdominal circumference reached 95 cm. According to the patient, it was a result of reduced physical activity during the COVID-19 pandemic and restrictions. In March 2022, an ultrasound follow-up examination of hepatic haemangiomas revealed newly diagnosed hepatic steatosis. The patient underwent transient elastometry and steatometry using FibroScan: METAVIR fibrosis stage F0 and NAS steatosis stage S3. Matabolism-associated (non-alcoholic) fatty liver disease (MAFLD/NAFLD) was diagnosed. The patient was recommended to do more physical exercises; UDCA 14.6 mg/kg and vitamin E were added to the therapy.

Discussion

Epidemiological data cannot provide deep insight into the actual incidence of esophageal dyskinesia because of under-diagnosis due to unclear oligosymptomatic course of disease and resulting late diagnosis with low body weight and malnutrition. Besides, quite often dyskinesias are confused with GERD. The incidence rises with age; middle-aged and elderly women are more susceptible to the disease. The incidence of a combination of GERD and esophageal dyskinesia is unknown due to a limited studies. It is known that in patients with confirmed GERD with resistance to PPI therapy, the incidence of impaired esophageal motility is up to 75 % [4].

In our case study, at the onset of disease in a 27-yearold patient, retrosternal pain was thought to be a symptom of peptic esophagitis revealed during EGRS. It is worth mentioning that the patient denies heartburn, dysphagia; however, the character of pain, i.e., worsening with meals, drinks, in prone position, are typical of esophagus pathologies. Standard GERD therapy regimen did not have any effect, and diagnostic search continued; cardiac and neurological disorders were excluded. Esophageal achalasia was suspected despite the absence of dysphagia observed in 99% of patients with esophageal achalasia [3]. Gastric manometry did not reveal any signs of esophageal achalasia: the integrated LES relaxation pressure was not increased (IRP > 15 mm Hg) and there were no contraction disorders present. According to clinical recommendations on esophageal achalasia, conservative therapy with calcium channel blockers or nitrates can have some effect in this pathology; however, it is just a temporary measure, while the primary management of esophageal achalasia is cardia dilatation, which is effective in 60-85 % [3]. Nevertheless, instead of further diagnostic search and selection of alternative conservative therapy, the patient underwent cardia dilatation which did not have any positive effect. It is worth noting that at this stage the therapy with calcium channel blockers or nitrates was not considered.

During his first visit to the clinic in 2019, the patient underwent a comprehensive examination of esophagus (including EGDS, esophagography, pH-impedancemetry, manometry), and the results came controversial.

EGDS, which is not a method of choice for esophageal dyskinesia diagnosis, is important to exclude organic disorders. In this case study, EGDS did not reveal any abnormalities which could be a sign of esophageal dyskinesia (dilated esophageal lumen, constrained endoscope passage, cardia obstruction, etc.). Cardia insufficiency, peptic esophagitis, superficial gastritis, duodenitis, and duodenogastric bile reflux were observed.

Esophagography confirmed gastroesophageal reflux, peptic esophagitis, and duodenogastric reflux. There were no typical signs of DES, however, this diagnosis cannot be ruled out: according to literature, abnormalities are observed only in 60 % of patients, while pathognomonic changes ("corkscrew" or "string of beads" esophagus) is

reported in less than 5% of cases [5]. Radiographic evidences of esophageal achalasia (cardia spasm and dilated esophagus) were not observed.

Manometry revealed inefficient esophageal motility: hypokinetic dyskinesia with clinical signs of regurgitation, dysphagia, feeling of weight in epigastrium. The patient denied these symptoms, his only complaint (retrosternal pain) was typical of hyperkinetic forms, since it is caused by spastic muscle contractions. It is worth mentioning that gastric manometry is a golden standard in esophageal dyskinesia diagnosis; however, The Chicago Classification of Esophageal Motility Disorders (v. 3, 2015) used at that time is useful to diagnose primary motility disorders, whereas secondary changes have no clear validated criteria. The report on The Chicago Classification of Esophageal Motility Disorders (v. 4, 2021) emphasises the role of manometry in differentiation between disorders which allow making a final diagnosis (for instance, achalasia) and other phenomena that are insignificant for the diagnosis and that require clinical interpretation [6]. In this case study, manometry allowed ruling out achalasia, a mandatory criteria of which is increased integrated LES relaxation pressure (IRP) of over 15 mm Hg.

24-hour esophagus pH-impedancemetry demonstrated normal acidic refluxes and time when pH was below 4; however, there were 32 alkaline refluxes, which correlated with EGDS results of duodenogastric bile reflux

It is worth mentioning that during EGDS procedures the patient did not have any pain, and it can be an indirect evidence of neuroreflex nature of esophageal spasm and can explain the absence of typical abnormalities observed during manometry. The same situation was observed during the initial examination in 2016: the patient did not have any pain during pH-impedancemetry and manometry.

To sum up the instrumental assessment results, it is worth noting that, despite their specificity, the existing diagnostic methods are not always useful for correct diagnosis, since there are no validated diagnostic criteria for any type of esophageal dyskinesia [6]. These methods are auxiliary; diagnosis requires comparative analysis of results of the mentioned instrumental assessments with clinical manifestations [6].

Table 1 presents primary clinical and instrumental characteristics of the patient as well as DES and esophageal achalasia criteria which were used in differential diagnosis [2, 3].

It seems to be possible to develop a practical algorithm for diagnostic search in patients with non-cardiac retrosternal pain. The primary method should be EGDS (if there are no contraindications) as it is highly informative and can help in ruling out organic disorders: esophageal cancer and cardiac cancer, gastroesophageal hernia, esophagitis, esophageal strictures. If the diagnosis is clear, therapy should follow the current recommendations; if no effect is observed or if information is limited, barium esophagography should be performed. The diagnostic search algorithm in case of non-cardiac retrosternal pain proposed by the authors is presented in Figure 4.

Table 1. Differential diagnosis of the patient based on the criteria for diffuse esophagospasm and achalasia cardia

Feature	Case	Diffuse esophagospasm	Achalasia cardia
Pain	++	++	+ (60%)
Dysphagia	-	+	++ (99%)
Regurgitation	-	+- (seldom)	+
Weight loss	-	+ (Late stages)	+ (Late stages)
Uncoordinated peristalsis, rosary symptom (X-ray)	-	+	-
Normal patency of the lower esophageal sphincter (X-ray)	+	+	-
Spasm of the cardia, expansion of the esophagus (X-ray)	-	-	+
Expansion of the esophagus, tightly closed cardia (endoscopy)	-	-	+
An increase in the total relaxation pressure of the lower esophageal sphincter >15 mm Hg. (high-resolution manometry)	-	-	++
Spasmodic contractions (high-resolution manometry)	-	+-	+
Number of acid refluxes above normal (pH monitoring)	-	+-	-
The effect of a calcium channel blocker	++	++	+
The effect of PPI	-	+	-

 $\textbf{Note:} \ \textbf{X-ray} - \textbf{X-ray} \ with \ \textbf{barium contrast;} \ \textbf{PPI} - \textbf{proton pump inhibitors}$

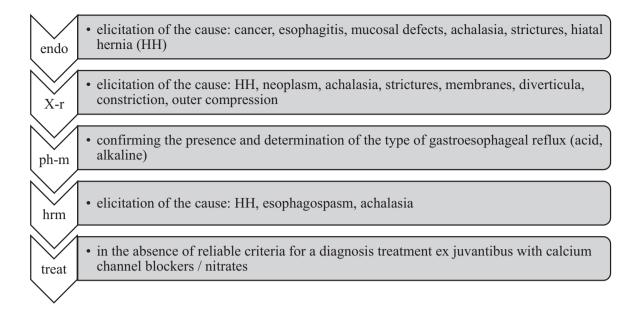


Figure 4. Diagnostic search algorithm in the presence of non-cardiac retrosternal pain.

Note: Endo — endoscopy; X-r — X-ray with barium contrast; pH-m — pH-monitoring; hrm — high-resolution manometry; treat — treatment

In this case study, this is efficient calcium channel blocker therapy that allowed confirming hyperkinetic esophageal dyskinesia — diffusive esophagism with GERD.

It is worth mentioning that at the onset of disease in 2013 and when the patient came to the clinic in 2019, he did not have any metabolic disorders; however, in March 2022 overweight and NAFLD were observed; these are frequent comorbidities of GERD with understudied relations [7, 8]. A number of studies are dedicated to the correlation between these disorders; in a majority of cases, the question is an increased risk of GERD in patients with fatty liver disease [7, 8], the pathologic relation between which is caused by overweight. In this case study, GERD developed well before, when the patient was a young man, while metabolic disorders appeared later and might have been triggered by forced limitation of physical activity.

Conclusion

Esophageal achalasia and diffusive esophagism are diagnosed relatively rarely and are understudied conditions. Retrosternal pain requires differential diagnosis to rule out myocardial or musculoskeletal disorders; however, a correct diagnosis is not an easy task even when extra-oesophageal pathology has been ruled out. Highly specific modern methods for esophagus pathology diagnosis can return controversial results that do not correlate with one another nor match clinical manifestations. This case study of a young patient with a long-lasting history of resistant retrosternal pain emphasises the need in a comprehensive examination and assessment of clinical and instrumental results for practical purposes, as

well as development of more clear criteria for scientific confirmation or exclusion of these diagnoses. Also, the relationship between esophagus involvement and metabolic disorders, specifically NAFLD, is of practical and scientific significance.

Вклад авторов

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Author Contribution

and approved the final version of the article before publication Ishchenko A.Yu. (ORCID ID: https://orcid.org/0000-0002-0730-3800. SPIN-code: 1624-2182): case management, article design development, creating the text of the manuscript, review of publications on the topic of the article, approval of the final version, taking responsibility for all aspects of the study, the integrity of all parts of the article and its final version

All the authors contributed significantly to the study and the article, read

Galushko M.Yu. (ORCID ID: https://orcid.org/0000-0001-8263-723X): preparation and editing of the text, resource providing for the research, approval of the final version, taking responsibility for all aspects of the study, the integrity of all parts of the article and its final version

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