AMYLOIDOSIS OF THE GASTROINTESTINAL TRACT. CLINICAL CASES

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ABSTRACT

Amyloidosis is a group of diseases characterized by extracellular deposition of fibrillar protein (amyloid) in tissues and organs, consisting of β-sheet plates. The clinical manifestations and the endoscopic picture of amyloidosis are diverse and not very specific, which makes it difficult for specialists to make a diagnosis. The most common manifestations from the gastrointestinal tract are observed in AL-amyloidosis. The morphological diagnosis is made by detecting the characteristic apple-green birefringence in polarized light after staining with Congo red. This article presents clinical cases of diagnosis of amyloidosis of the gastrointestinal tract and modern literature data.

Key words: AA-amyloidosis, AL-amyloidosis, amyloid, amyloidosis, endoscopy.

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INTRODUCTION

Amyloidosis is a group of diseases characterized by extracellular deposition of fibrillar protein (amyloid) consisting of β-pleated sheets in tissues and organs [1]. The diagnosis is made when characteristic apple-green birefringence is detected in polarized light after the congo is stained red [2, 3]. According to the nomenclature adopted by the International Society of Amyloidosis, the first letter A stands for amyloid, and the following letters refer to the precursor protein: A (amyloid A-protein), L (immunoglobulin light chains), TTR (transstyretin), β2M (β2-microglobulin), B (B protein), IAPP (islet amyloid polypeptide), etc. [4].

Primary AL amyloidosis is the most common form with generalized deposition of excess light chains, is associated with plasma cell dyscrasia and has the maximum GIT lesion [5]. AL amyloidosis is caused by plasma cell dyscrasia, which may occur on its own or be associated with multiple myeloma [6].

Secondary AA amyloidosis is associated with infectious, inflammatory or less often neoplastic diseases. The mechanism of organ damage is that against the background of the inflammatory process, an increase in the acute phase protein (SAA) occurs, part of which is deposited in organs and tissues in the form of amyloid fibrils [5]. This pathology occurs in rheumatoid arthritis, Crohn's disease, ankylosing spondylitis, Reiter's syndrome, psoriasis, progressive systemic sclerosis, primary biliary cirrhosis, stromal tumors of the gastrointestinal tract and other diseases.

Familial amyloidosis (ATTR) has several subtypes. The most common hereditary autosomal dominant ATTR amyloidosis is due to mutations in the transstyretin molecule (which is produced in the liver) or age-related disorder of transstyretin tetramers secretion by the liver. In both cases, transstyretin tetramers break down to monomers with pronounced protein conformation instability [7].

CLINICAL MANIFESTATIONS

Damage from the gastrointestinal tract is more often manifested in AL amyloidosis. In the oral cavity, the most common manifestation is macroglossia, which can cause sleep apnea, speech disorders, oral dysphagia and chewing problems [8]. The main symptoms of the esophagus are: dysphagia, chest pain, heartburn and vomiting [9]. Manometric changes can also be observed in the esophagus, which are manifested mainly in AL amyloidosis. Low pressure in the lower esophageal sphincter and a decrease in the amplitude of contractions are determined, while the upper sphincter of the esophagus and pharynx work normally [10]. This picture is observed with achalasia. Unlike idiopathic achalasia, patients develop symptoms quickly enough and lose weight drastically [11]. In patients with amyloidosis, gastric damage is manifested by nausea, vomiting, epigastric pain. Complications in the form of perforations, fistulas and bleeding are also possible [12, 13].

The greatest degree of amyloid deposition is observed in the small intestine, in intima and adventitia of blood vessels, thereby affecting the vascular network. When the wall of a vessel thickens, its lumen narrows down and eventually gets completely clogged and thrombosed, which leads to ischemia and heart attack [14]. Also, amyloid is deposited between the muscle fibers, causing atrophy of neighboring fibers due to compression, so that eventually the entire muscle layer is replaced by amyloid. Clinical manifestations in patients with small intestine amyloidosis include: diarrhea, steatorrhea, protein loss, bleeding, obstruction, perforation, invagination, pneumatosis, constipation, and pseudoobstruction [5].

Clinical manifestations of large intestine amyloidosis can mimic diseases such as inflammatory bowel disease [15], malignant neoplasms [16], ischemic colitis [17, 18] and collagen colitis [19].

DIAGNOSTICS

An important aspect in the diagnosis of amyloidosis of the gastrointestinal tract is the histological examination of biopsy species with the detection of the characteristic apple-green birefringence in the foci of the amyloid clusters when examined in polarized light. It should be noted that each particular amyloid protein has a predominant place of deposition in the gastrointestinal tract. AL amyloid, Aβ2mg (β2-microglobulin) and ATTR tend to be deposited in the submucosal layer, while AA amyloid tends to be deposited in the surface layers [20, 21]. The largest study to determine the most frequent localization of gastrointestinal lesions was conducted in 2016 by Freudenthaler et al. They analyzed 542 patients with amyloidosis and gastrointestinal lesions. As a result, it was revealed that the frequency of amyloid deposits during biopsy was 38% in the colon, 23% in the stomach, 17% in the rectum, 16% in the duodenum and 6% in the jejunum or ileum [21-23]. In another major retrospective study, Cowan et al. examined 2334 patients, in 76 (3.3%) patients biopsy diagnosed gastrointestinal tract lesions; amyloid fibrils were identified in 50% in the small intestine, 44% in the stomach and 32% in the large intestine [24]. After analyzing a number of studies reflecting the degree of amyloid deposition, it can be concluded that the small and large intestines may be a suitable place for endoscopic biopsy, as they are the most frequent local-

ization of amyloid deposits compared to other parts of the gastrointestinal tract.

Endoscopic manifestations of gastrointestinal amyloidosis are diverse and nonspecific. Erosions, ulcerations, mucosal granularity, polyps, thickening of the gastric folds, submucosal hematomas and petechial elements can be determined on the mucous membranes [5, 20]. Eventual complications may also include: colon dilation [25, 26], pseudo-obstruction [27—29], strictures, rectal bleeding [25—30], inversion [26] and perforation [31]. One of the retrospective surveys that studied the correlation between the location of amyloid deposits and its endoscopic appearance showed that patients with superficial endoscopic lesions usually have amyloid deposits in the lamina propria, while patients with granular or thickened mucosa during endoscopy have amyloid deposits in the submucosa [32, 33].

Iida et al. conducted a study assessing the differences in positive results of endoscopic biopsy in patients with systemic amyloidosis accompanied with gastrointestinal tract lesion; biopsy samples were taken both from altered areas of the mucous membrane, and from unaltered ones. The percentage of positive gastric biopsies was significantly higher in patients with endoscopic data than in patients without such results (80 vs. 44%), a similar trend was observed in the small intestine and large intestine. However, in the duodenum and rectum, there was no reliable difference in the percentage between patients (89 vs 90%) (Table 1) [21].

The diagnosis of amyloidosis of the large intestine uses high-resolution and narrow-spectrum endoscopy. Rectal amyloidosis is characterized by mucosal granularity and grayish-green nodules when using narrow-spectrum endoscopy, probably due to the deposition of amyloid protein in the lamina propria. This method can help distinguish rectal amyloid deposits from neoplastic lesions [34, 35].

TREATMENT

Currently, there are no generally accepted protocols for the treatment of gastrointestinal amyloidosis. Treatment depends on the causes, clinical manifestations and type of amyloid protein.

The therapy of AL amyloidosis is aimed at reducing the production of monoclonal immunoglobulin light chains by suppressing the proliferation of plasma cells. Combined regimens based on bortezomib, melphalan and dexamethasone are considered to be first-line therapy, especially in patients with a high risk of rapid progression. As remission is achieved in some patients, high-dose chemotherapy with autologous stem cell support is used, which allows for long-term remission. Strict selection of patients is necessary due to multiple contraindications [36].

Against the background of effective inflammation control, the production of the precursor protein is suppressed, which is the main goal for the treatment of AA amyloidosis. As a result, the production of serum amyloid protein A and the acute phase reaction decrease.

Biologics (including TNF inhibitors, interleukin-6, rituximab) and cytostatics play a key role in the treatment of major chronic inflammatory conditions, such as rheumatoid arthritis, Crohn's disease, psoriasis etc. Colchicine is the remedy of choice for the treatment of AA amyloidosis in recurrent illness and severe progressive gout. When used constantly, it is possible to completely stop the recurrence of seizures in most patients and slow down the development of amyloidosis in them; lifelong colchicine intake is possible [36, 37]. For the treatment of hereditary amyloidosis, it is necessary to eliminate the source of the genetically modified protein production. The liver produces most of the TTR protein circulating in the body. Orthotopic liver transplantation can be used to significantly reduce the production of pathogenic protein, since the diseased liver,

Table 1. Differences in the frequency of positive results in endoscopic biopsy of systemic amyloidosis with gastrointestinal lesion in patients with or without endoscopic data

Indicators	Stomach	Duodenum	Small intestine	Large intestine	Rectum
With endoscopic data	76,00 %	89,00 %	50,00 %	89,00 %	88,00 %
No endoscopic data	44,00 %	90,00 %	25,00 %	33,00 %	78,00 %
P-value	0.02	0.96	0.47	0.02	0.6

which secretes the mutated form of TTP, is replaced by the liver, which secretes normal protein [38].

PROGNOSIS

The prognosis depends on the type of amyloid, its etiology and the degree of organ damage. AL amyloidosis is associated with the most unfavorable outcomes. Typically, in patients with this type of amyloidosis the gastrointestinal tract is involved and they have a more severe course and a lower survival rate. In AA-amyloidosis, the level of acute-phase reactive protein amyloid A in the blood serum correlates with mortality. Although gastrointestinal complications may worsen the overall disease, they are not usually a cause of death [3].

CLINICAL OBSERVATIONS

In this report, we present two cases of gastrointestinal amyloidosis identified at the Almazov National Medical Research Centre of the Ministry of Health of Russia. The main purpose of the demonstration is to show the features of the endoscopic picture of gastrointestinal amyloidosis.

Patient J., 44 years old, was admitted to the clinic with complaints of abdominal pain, vomiting with blood streaks, and she also noted several episodes of vomiting "spent coffee grounds". During an outpatient examination, gastrointestinal amyloidosis was suspected. Given the increase in symptoms, the appearance of

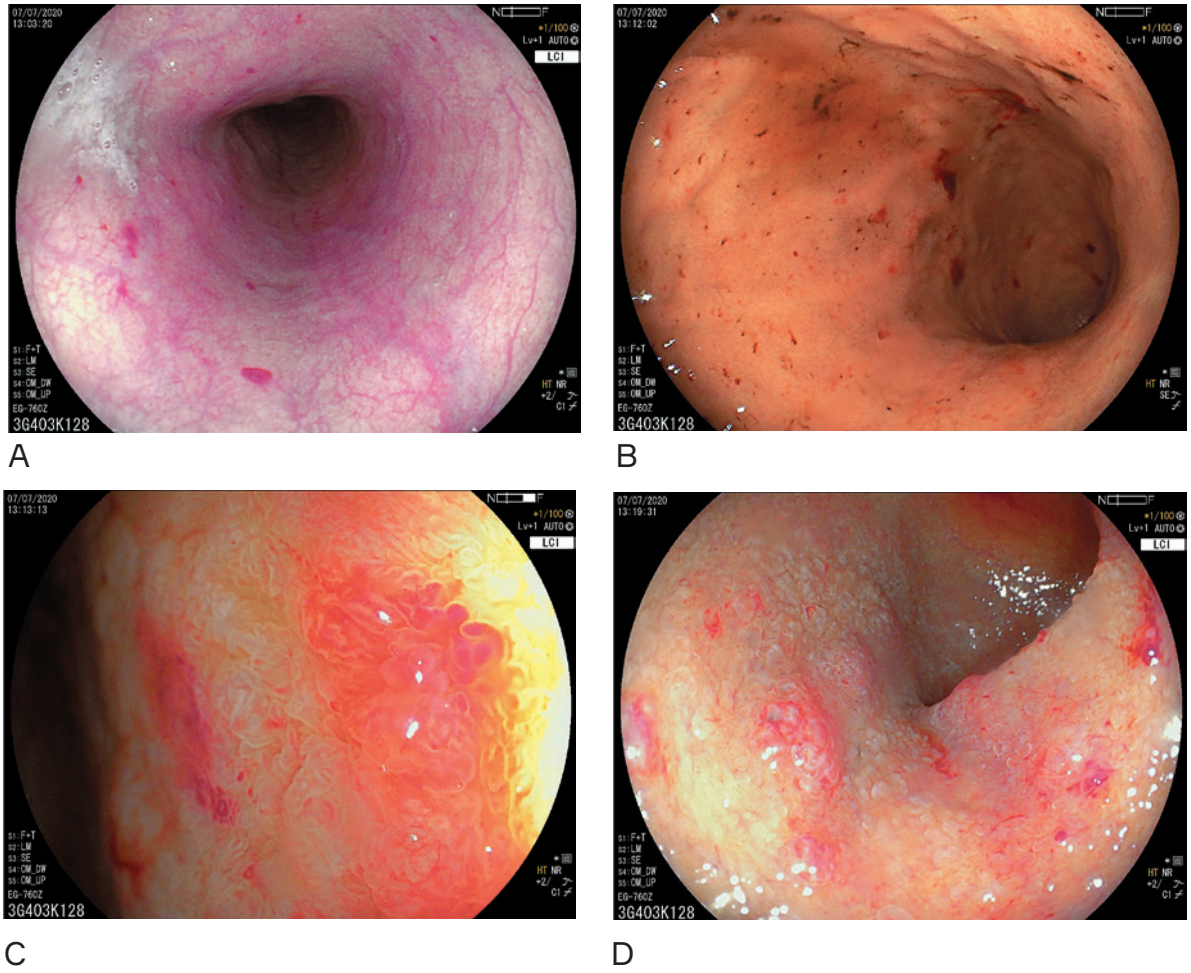
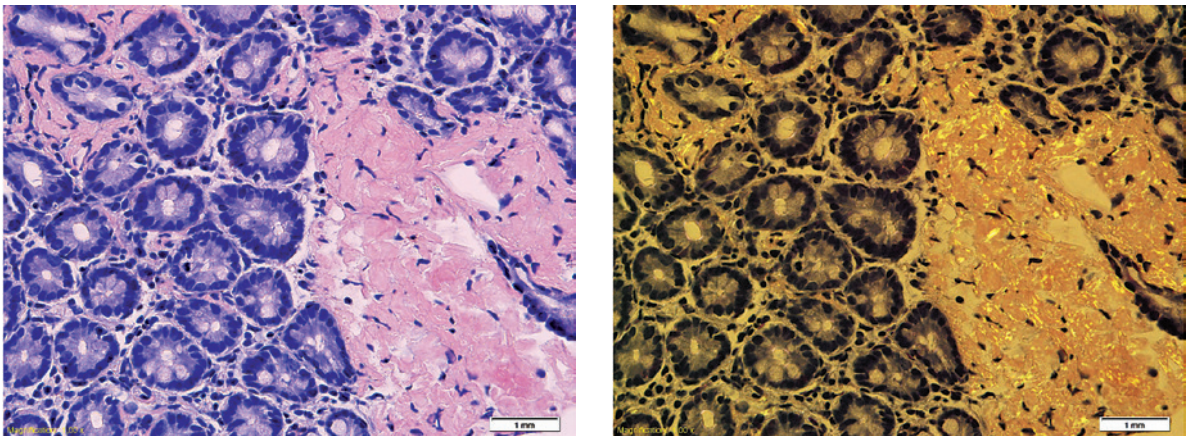


Fig. 1. AL amyloidosis in a woman, 44 years old, endoscopic picture:

A — single red flat spots with clear borders and a smooth surface, 2-4 mm in size are determined on the mucous membrane of the esophagus; when examined in LCI mode using ZOOM, the submucosal location of these elements is presumed;

B, C — the mucous membrane in the body and antrum is contact-vulnerable, with multiple fixed clots of small size, black color, as well as hemorrhagic erosions, mainly in the body of the stomach; when examined in LCI, BLI, ZOOM modes, the mucosa is represented by foci of atrophy and hyperplasia, with signs of intestinal metaplasia; the mucosa relief does not correspond to the gastric one, it is asymmetrical, capillary dilatation is determined; pronounced contact vulnerability is drawing attention;

D — the duodenal bulb is focally hyperemic, contact-vulnerable, the relief pattern is asymmetric

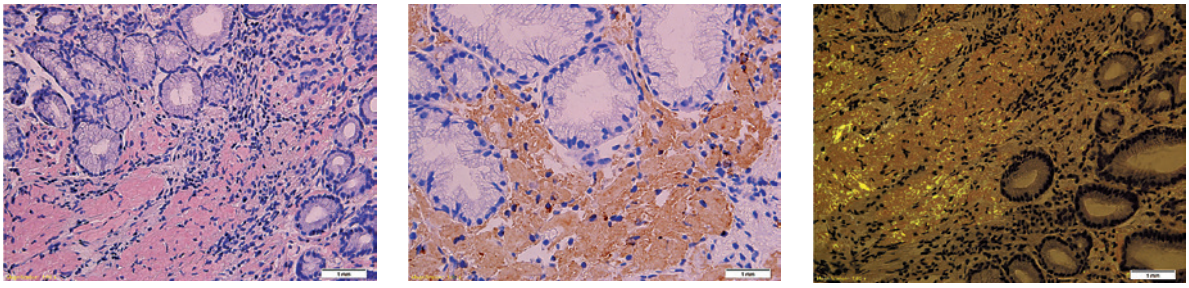


A B

Figure 2. AL amyloidosis of the duodenum in a woman, 44 years old, histological examination:

A — amyloid in the lamina propria of the duodenum, color — hematoxylin-eosin, magnification ×600;

B — polarized light study, staining with Congo red, magnification ×600



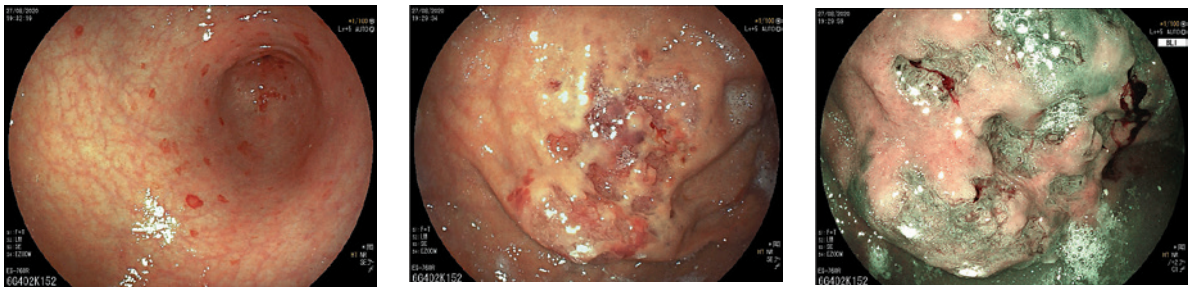
A B C

Figure 3. Gastric AL amyloidosis in a woman, 44 years old, histological examination:

A — amyloid in the interstitia of the lamina propria of the gastric mucosa, hematoxylin-eosin stain, magnification ×600;

B — staining with Congo red, magnification ×600;

C — polarized light study, staining with Congo red, magnification ×600



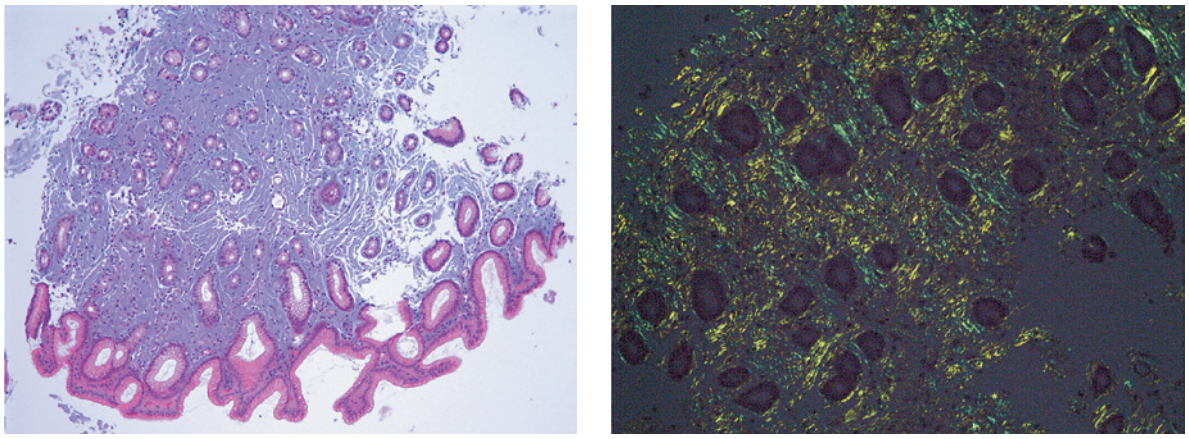
A B C

Figure 4. Gastric AL amyloidosis in a woman, 55 years old, endoscopic picture:

A — in the body and antrum, areas of bright hyperemia are determined against the background of atrophy;

B — in the area of the fundus of the stomach, a contact-vulnerable area of the altered mucosa with structureless foci is determined;

C — in the narrow spectrum mode, the pattern is irregular, sometimes absen



A B

Figure 5. Gastric AL amyloidosis in a woman, 55 years old, histological examination:

A — biopsy of the gastric mucosa with fibrosis of the lamina propria, hematoxylin-eosin stain, alcian blue, magnification ×100;

B — biopsy of the gastric mucosa, Congo red stain, magnification × 200, polarization microscopy; amyloid deposits glow apple-green in polarized light

"anxiety symptoms" and the unverified diagnosis of amyloidosis, the patient with suspected monoclonal gammopathy was hospitalized in the clinic for additional examinations and determination of further treatment tactics. A laboratory and instrumental examination revealed systemic AL amyloidosis associated with multiple myeloma.

During endoscopic examination in the esophagus, single red flat spots with a smooth surface of 2—4 mm in size were determined on the mucous membrane. When viewed in LCI mode using ZOOM, the submucosal location of these elements was presumed. The stomach revealed pronounced contact vulnerability of the gastric mucosa, multiple fixed clots, hemorrhages, and erosions. In the duodenal bulb, the mucous membrane was contact-vulnerable, its relief pattern was asymmetrical. A multifocal biopsy was performed, which resulted in the detection of amyloid deposits (Figures 1—3).

Patient Zh., 55 years old, was admitted to the clinic with complaints of mammary gland formations. During an extensive laboratory and instrumental examination, the patient was diagnosed with Bence Jones myeloma with Carr light chain secretion, st. I A, ISS. A histological examination of a breast biopsy was performed, in which a diffuse massive deposition of amyloid was determined. A monoclonal component (Bence Jones protein) was detected in the urine, and the quantification of the light chains of kappa lambda in the urine showed secretion up to 6 mg/dL (above the reference values). MRI of the heart revealed a pathological accumulation of contrast agent in the myocardium of the left ventricle, right ventricle and atria, which may be due to the manifestation of amyloidosis. The patient was assigned a screening endoscopic examination of the upper gastrointestinal tract to assess the mucosa. When examined in the area of the fundus of the stomach, an altered, contact-vulnerable mucosa with unstructured foci of red color was determined. Biopsy of the altered areas histologically revealed amyloid deposition with an apple-green glow when stained with Congo red (Figures 4, 5). During hospitalization, based on the data obtained, the diagnosis was made: Bence Johns myeloma with Carr light chain secretion, st. I A, ISS — 1 st. Primary systemic AL amyloidosis with damage to the heart, gastrointestinal tract and mammary glands.

As these cases show, one of the patients had obvious symptoms from the gastrointestinal tract, which helped diagnose amyloidosis. In the case of another patient, no gastrointestinal complaints were observed, but the vigilance of clinicians and a thorough examination during the endoscopic examination also helped not to miss this disease.

CONCLUSIONS

Amyloidosis is a severe systemic disease that in some cases affects the gastrointestinal tract. The endoscopic picture of of the gastrointestinal amyloidosis is not very specific and has no pathognomonic signs. This disease has an unfavorable prognosis, so its early diagnosis is important. Endoscopic examination requires a thorough examination of the mucous membrane of the gastrointes-

tinal tract both in white light and using additional modes (enlargement, narrow-spectrum mode). If amyloidosis of the gastrointestinal tract is suspected, it is necessary to take material not only from the abnormal areas, but also from the unaltered ones. Taking into account the most frequent detection of amyloid deposits in the duodenum and rectum, it is recommended to take samples of the mucous membrane from these departments.

Conflict of interest

The authors declare no conflict of interest.

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