



A Case of Primary Amyloidosis Involving Liver, Stomach, Intestines, and Heart without Evident Kidney Involvement

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Aim. Systemic amyloidosis caused by the synthesis and deposition of immunoglobulin light chains (AL amyloidosis) is a relatively rare disease that involves heart, kidneys, peripheral nervous system, gastrointestinal tract, and has a large number of various clinical manifestations. We present a clinical case of systemic AL amyloidosis with a predominant involvement of liver, stomach, intestines, and heart in a Caucasian female.

Key points. A Caucasian woman presented to clinic with severe general weakness, abdominal pain, diarrhea, sudden weight loss, and palpitation. Initial examination revealed a duodenal bulb ulcer complicated by bleeding and polyps in the retrobulbar part of duodenum. Decreased hemoglobin levels, elevated levels of alkaline phosphatase, gamma-glutamyltransferase, and N-terminal prohormone of brain natriuretic peptide, signs of heart failure with preserved ejection fraction, and hepatomegaly became the basis for a clinical suspicion of AL amyloidosis and puncture liver biopsy. Histochemical and immunohistochemical studies of liver, stomach, and duodenum biopsy specimens confirmed AL amyloidosis. Timely diagnosis made it possible to conduct a specific therapy with melphalan plus dexamethasone, get a satisfactory response and improve the patient's condition.

Conclusion. A thorough examination of patients along with a pathomorphological and immunohistochemical study of the biopsy specimens is the basis for confirming the diagnosis of AL amyloidosis, selecting the proper therapy, improving the condition of patients and their survival.

Keywords: primary AL amyloidosis, immunoglobulin light chain amyloidosis

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Случай первичного амилоидоза с вовлечением печени, желудка, кишечника и сердца, который не сопровождался поражением почек

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Цель. Системный амилоидоз, вызванный образованием и отложением легких цепей иммуноглобулинов (AL-амилоидоз), представляет собой относительно редкое заболевание с поражением сердца, почек, периферической нервной системы, желудочно-кишечного тракта, что обуславливает многообразие его клинических проявлений. Мы представляем случай системного AL-амилоидоза с преимущественным поражением печени, желудка, кишечника и сердца без вовлечения почек у женщины европеоидной расы.

Основное содержание. Пациентка предъявляла жалобы на выраженную общую слабость, боль в животе, диарею, быструю потерю массы тела и сердцебиение. Эзофагогастродуоденоскопия выявила кровоточащую язву двенадцатиперстной кишки и ретроbulбарный полипоз. Содержание гемоглобина было снижено, а уровни щелочной фосфатазы, гамма-глутамилтранспептидазы и N-терминального предшественника мозгового натрийуретического пептида были повышены. Также имелись признаки сердечной недостаточности с сохраненной фракцией выброса и гепатомегалия. Была проведена биопсия печени, желудка и двенадцатиперстной кишки.

Гистохимическое и иммуногистохимическое исследование биоптатов подтвердило диагноз AL-амилоидоза. Проведено лечение мелфаланом и дексаметазоном с удовлетворительным эффектом.

Заключение. Тщательное клиническое обследование пациента вместе с патоморфологическим и иммуногистохимическим исследованиями биоптатов позволили установить верный диагноз и назначить адекватную терапию, что улучшило состояние пациента.

Ключевые слова: первичный AL амилоидоз, амилоидоз легких цепей иммуноглобулинов

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Introduction

The modern definition of amyloidosis refers to a group of diseases caused by aggregation of a certain fibrillar glycoprotein known as amyloid in the organs and tissues [1]. Unlike other fibrillar stromal proteins, amyloid has the following characteristic features: birefringence under polarized light after pre-staining with Congo red and discoloration of amyloid deposits from red to apple-green [1, 2].

One of the forms of systemic amyloidosis, which is associated with aggregation of amyloid formed from immunoglobulin light chains (AL amyloidosis), is caused by the abnormal plasma cell clone in the bone marrow, or so-called B cell dyscrasia [1]. Completion of the phases of amyloid nucleation and elongation in AL amyloidosis is a kind of impetus for its dissemination or spread to almost all organs and tissues except brain [1–3]. Amyloid formation and deposition are not metabolically neutral processes as they are associated with tissue damage and organ dysfunction due to the cytotoxic properties of prefibrillar oligomers, which form amyloid fibrils, as well as the direct adverse mechanical effect of amyloid on tissues, their architectonics and functions [1, 3, 4].

Target organs in AL amyloidosis include heart, kidneys, gastrointestinal tract, and peripheral nervous system; this accounts for the diversity of clinical manifestations. Suspected AL amyloidosis may be the reason for biopsy of fat pad, bone marrow, and other organs, including duodenum, stomach, colon, rectum, esophagus, and liver [5–7]. Once suspected and a monoclonal component is detected, confirmation requires more expensive microscopic studies to diagnose amyloidosis, such as mass spectrometry (“gold standard”), immunogold electron microscopy, immunofluorescence, and immunohistochemistry [7]. The guidelines on diagnosis and treatment of AL amyloidosis were published recently [8–10].

Clinical case

A 44-year-old woman presented to the Center of Reconstructive and Restorative Medicine (University Clinic) of Odessa National Medical University with complaints of severe general weakness; belting abdominal pain, aching and constant in its nature; bloating; stomach being “cold and strange”. The patient

suffered from bowel disorders — frequent and “uncontrolled” intestinal discharge, 23 kg weight loss within 9 months; occasionally — increased blood pressure, palpitation.

The patient was feeling ill for about 8 months, when frequent liquid intestinal discharge first appeared (up to 15 times a day). She underwent the outpatient treatment with loperamide, antimicrobials (phthalylsulfathiazole, nifuroxazide), and probiotics with positive effect. Such episodes occurred 2–3 times a month. At the same time, hemorrhoids worsened, which was also treated on an outpatient basis.

The patient felt weak against the background of recurrent exacerbations of hemorrhoids and diarrhea. Anemia with hemoglobin level about 80 g/L was detected 2 months after the onset of the disease.

Stomach radiography with oral contrast was carried out because patient refused to perform esophagogastroduodenoscopy. The results were: edge filling defect is revealed in horizontal position in the gastric fundus with transition to the upper third along the greater curvature; mucosa folds are unevenly thickened and tortuous in the fundus, body, along the greater curvature, in the antrum, the relief is deformed; an uneven accumulation of contrast (a small ulcer along the upper edge) in the antrum; external compression due to adjacent organs.

Patient's condition was gradually deteriorating. She had a consultation with a gastroenterologist 7 months after the onset of symptoms. Esophagogastroduodenoscopy was strongly recommended.

Esophagogastroduodenoscopy: chronic ulcer of a duodenal bulb complicated by bleeding; erythematous gastroduodenopathy; cicatricial ulcer deformation of the duodenal bulb; lower esophageal sphincter insufficiency; polypoid proliferation in the retrobulbar part of duodenum (biopsy performed). Biopsy preliminary conclusion: amyloidosis of the duodenum mucosa.

The patient was admitted to our Clinic with these results 8 months after the onset of the disease.

Physical examination showed the expansion of the left border of relative cardiac dullness to the left midclavicular line, rhythmic and muffled heart sounds, a short systolic murmur heard at the apex, blood pressure of 115/75 mm Hg, heart rate of 92 beats per min, enlarged abdomen, sensitive large

intestine segments, and enlarged liver with its border 2.5 cm lower the costal arch.

Results of laboratory tests had the following features: anemia with hemoglobin levels of 92–106 g/L and red blood cell count of $(3.29\text{--}3.52) \times 10^{12}/\text{L}$, neutrophilic shift of the leukocyte formula with a normal leukocyte count. Acute phase markers were increased: erythrocyte sedimentation rate (Westergren method) up to 120 mm/h and C-reactive protein up to 47 mg/mL (normal level: less than 6 mg/mL). Rheumatoid factor was 27.6 IU/mL (normal level: less than 15 IU/mL).

Biochemical test revealed a decrease in serum total protein levels to 64.7 g/L (normal range: 65–85 g/L) due to a decrease in serum albumin level 34.6 g/L (normal range: 35–50 g/L), elevated aspartate aminotransferase of 47 IU/L (normal level: less than 40 IU/L) with normal alanine aminotransferase levels, increased total bilirubin level 42.7 $\mu\text{mol/L}$ (normal range: 8.5–20.5 $\mu\text{mol/L}$) due to increased direct bilirubin level 34.1 $\mu\text{mol/L}$ (normal range: 0.9–4.3 $\mu\text{mol/L}$), as well as very high levels of gamma-glutamyltransferase (GGT) 437 IU/L (normal range: 9–39 IU/L) and alkaline phosphatase (ALP) 1367 IU/L (normal level: less than 105 IU/L).

Glucose and renal function tests were normal, uric acid levels were lowered to 117 $\mu\text{mol/L}$ (normal range: 140–340 $\mu\text{mol/L}$). Serum iron was decreased to 4.7 $\mu\text{mol/L}$ (normal range: 9.0–30.4 $\mu\text{mol/L}$), the blood levels of other biominerals (potassium, sodium, magnesium, phosphorus, chloride, calcium) were within normal range.

The biomarkers of heart injury (troponins, cardiac creatine phosphokinase, and lactate dehydrogenase) were within normal range, but N-terminal prohormone of brain natriuretic peptide (NT-proBNP) levels were elevated to 198 pg/mL (normal level: less than 125 pg/mL).

Electrocardiogram (Fig. 1): normal sinus rhythm; signs of impaired repolarization processes in the inferolateral part of the left ventricle and diffuse myocardial changes.

Echocardiogram (Fig. 2): left ventricular global function is not impaired, left ventricular ejection fraction is 67 %; signs of right ventricular volume overload; aortic atherosclerosis; signs of left ventricle walls concentric hypertrophy (A); no changes in cavity size (B); hyperechoic foci in the interventricular septum (C); grade 1 mitral valve regurgitation, grade 1 tricuspid valve regurgitation, mild pulmonary hypertension; signs of a mild hydropericardium (D). Considering the data from physical examination, the detected changes may be evidence of cardiac amyloidosis [11, 12].

Abdominal ultrasound examination revealed hepatosplenomegaly.

Computed tomography of the abdominal cavity and retroperitoneal space with intravenous contrast enhancement (Fig. 3) showed changes that may refer to liver amyloidosis [11]: mesenteric tissue is diffusely swollen and dense, with a large number of lymph nodes that are signs of mesenteric panniculitis; liver is enlarged, with clear smooth contours, diffuse uneven decrease in parenchymal density, mainly in the subcapsular areas, which is more evident in the venous phase (becomes homogeneous upon delayed phase); a thin strip of perihepatic effusion; signs of chronic pancreatitis.

Histopathological study of the duodenum (Fig. 4): edema, focal glandular atrophy, intraepithelial lymphocytes and neutrophilic leukocytes, cryptitis in occasional glands, focal squamous cell metaplasia, lymphohistoplasmacytic inflammatory cellular infiltrate of the stroma with polymorphonuclear leukocytes, focally with eosinophils and monocytes; a glandular polyp in one of the fragments (A). An uneven thickening is observed in the lamina propria due to the deposition of homogeneous eosinophilic masses and areas of sclerosis, microvascular vessels are dilated and full-blooded; positive brick-red focal masses are detected in the stroma, lamina propria, and walls of vessels of various sizes after Congo red staining (B). Upon immunohistochemistry, phenotyping of amyloid was carried out: AA amyloid – predominantly negative expression (C),

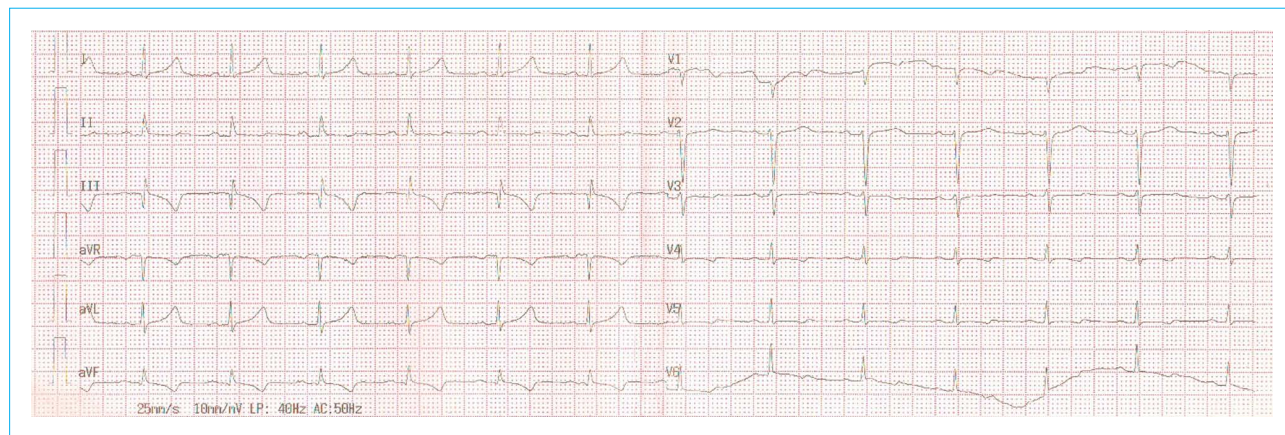


Fig. 1. Electrocardiogram of the patient. Diffuse myocardial changes

Рис. 1. Электрокардиограмма описываемого пациента. Диффузные изменения миокарда

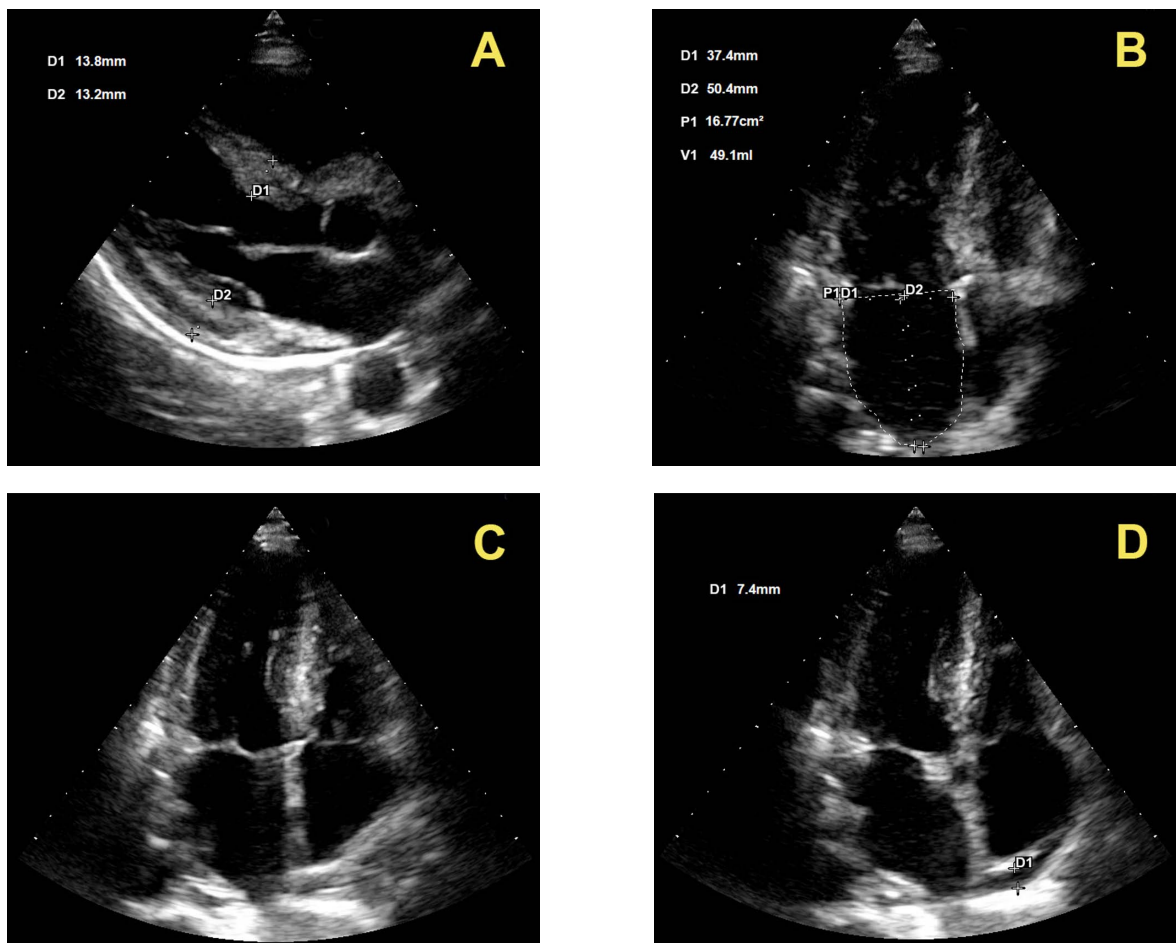


Fig. 2. Echocardiographic signs of cardiac amyloidosis in the patient: (A) left ventricular parasternal long axis view — increased thickness of left ventricle posterior wall (D2) and interventricular septum (D1); (B) apical 4-chamber view — myocardial hypertrophy with unchanged size of the heart cavities; D1, D2 — transverse and longitudinal dimensions of the left atrium; P1, V1 — calculated area and volume of the left atrium; (C) the same view — enhanced echo signal in the interventricular septum, typical “shiny” hyperechoic foci; (D) the same view — separation of pericardial sac layers up to 7.4 mm (D1) behind the right atrium

Рис. 2. Эхокардиографические признаки амилоидоза сердца у описываемого пациента: (А) парастеральный доступ, позиция по длинной оси левого желудочка: утолщение задней стенки левого желудочка (D2) и межжелудочковой перегородки (D1); (В) апикальный доступ, четырехкамерная позиция: гипертрофия миокарда без изменения размеров полостей камер сердца; D1, D2 — поперечный и продольный размеры полости левого предсердия; P1, V1 — вычисленные площадь и объем левого предсердия; (С) апикальный доступ, четырехкамерная позиция: усиленный эхосигнал от межжелудочковой перегородки; типичные «блестящие» гиперэхогенные очаги; (D) апикальный доступ, четырехкамерная позиция: сепарация листков перикарда до 7,4 мм (D1) позади правого предсердия

κ - and λ -light chains — positive expression in the stroma, lamina propria (the areas of homogeneous masses deposition), and blood vessel walls (D).

Pathomorphological diagnosis was: AL amyloidosis with dominating λ - and κ -light chains expression, mild focal AA amyloid expression; a moderate chronic duodenitis and glandular polyp with mild epithelial dysplasia.

Liver trephine biopsy (Fig. 5) revealed signs of the architectonics disorder due to the marked diffuse deposition of homogeneous eosinophilic masses in the stroma, which are replacing the liver parenchyma;

severe atrophy and degeneration of hepatocytes, some hepatocytes are hypertrophied and necrotic, others — with signs of apoptosis (A). Uneven marked dilatation of some parts of the portal tracts, mild focal lymphohistiocytic infiltrate along the portal tracts, perivascular and periductal fibrosis in sinusoidal vessels and depositions of eosinophilic masses; some bile ducts have signs of atrophy, vascular signs of sclerosis, others have thickened walls due to the deposition of eosinophilic masses (B).

After Congo red staining, positive brick-red masses were diffusely observed in the stroma and walls of vessels

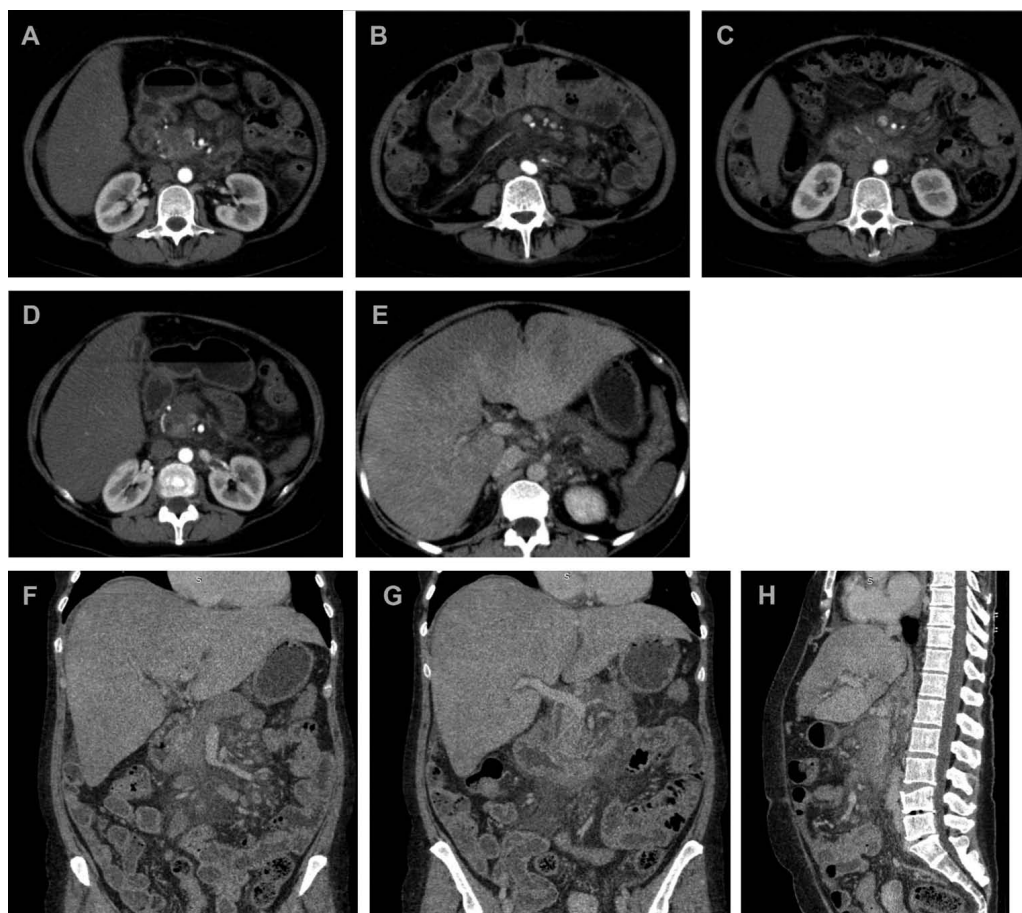


Fig. 3. Computed tomography of the abdominal cavity and retroperitoneal space with intravenous contrast enhancement: (A) aortic phase; stranding around the pancreatic head and in the retroperitoneal tissue; renal parenchyma is not thinned, of normal size, cortico-cerebral differentiation is preserved; (B) cord-like mesenteric root of the small intestine, mesenteric tissue is diffusely swollen and dense; increased number and size of mesenteric lymph nodes 10–12–15 cm — signs of mesenteric panniculitis; (C) duodenum walls are swollen, three-layered, slightly thickened, mostly in the descending and in the lower horizontal part; (D) tissue stranding around the gallbladder, its walls are neither thickened nor hypervascular; (E) portal phase; uneven contrast of the liver parenchyma, decreased liver density in the portal phase; the spleen is not enlarged; a thin strip of perihepatic effusion (4 mm); signs of chronic pancreatitis; (F) coronal projection, portal phase; the liver is enlarged (267×172×197 mm), with clear even contours, diffuse uneven decrease in parenchymal density, mainly in the subcapsular areas, which is more evident in the venous phase (becomes homogeneous upon delayed phase); mesenteric lymphadenopathy; the contours of the pancreatic head are indistinct; (G) duodenum — stranding of the tissue adjacent to the lower horizontal part; stranding of the parapancreatic tissue in the pancreatic body; (H) sagittal projection; stranding of the retroperitoneal tissue

Рис. 3. Компьютерная томография брюшной полости и забрюшинного пространства с внутривенным контрастным усилением: (А) аортальная фаза; тяжистость вокруг головки поджелудочной железы и в забрюшинной клетчатке; почечная паренхима не истончена, нормального размера, кортико-церебральная дифференцировка сохранена; (В) корень брыжейки тонкой кишки тяжистый, клетчатка брыжейки диффузно-отечная, плотная; увеличены число и размер брыжеечных лимфатических узлов (10–12–15 см), признаки мезентериального панникулита; (С) стенки двенадцатиперстной кишки отечны, трехслойные, слегка утолщены, преимущественно в нисходящей и нижней горизонтальной частях; (D) тяжистость клетчатки вокруг желчного пузыря, его стенки не утолщены и не гиперваскулярны; (Е) портальная фаза; неравномерное контрастирование паренхимы печени, снижение плотности печеночной ткани в портальной фазе; селезенка не увеличена; тонкая полоска выпота в околопеченочном пространстве (4 мм); признаки хронического панкреатита; (F) коронарная проекция, портальная фаза; печень увеличена (267×172×197 мм), с четкими ровными контурами, диффузное неравномерное снижение плотности паренхимы, преимущественно в подкапсульных областях, более выраженное в венозной фазе (становится однородным в отсроченной фазе); мезентериальная лимфаденопатия; контуры головки поджелудочной железы нечеткие; (G) двенадцатиперстная кишка — тяжистость клетчатки, прилегающей к нижней горизонтальной части; тяжистость парapanкреатической клетчатки в теле поджелудочной железы; (H) сагиттальная проекция; тяжистость забрюшинной клетчатки

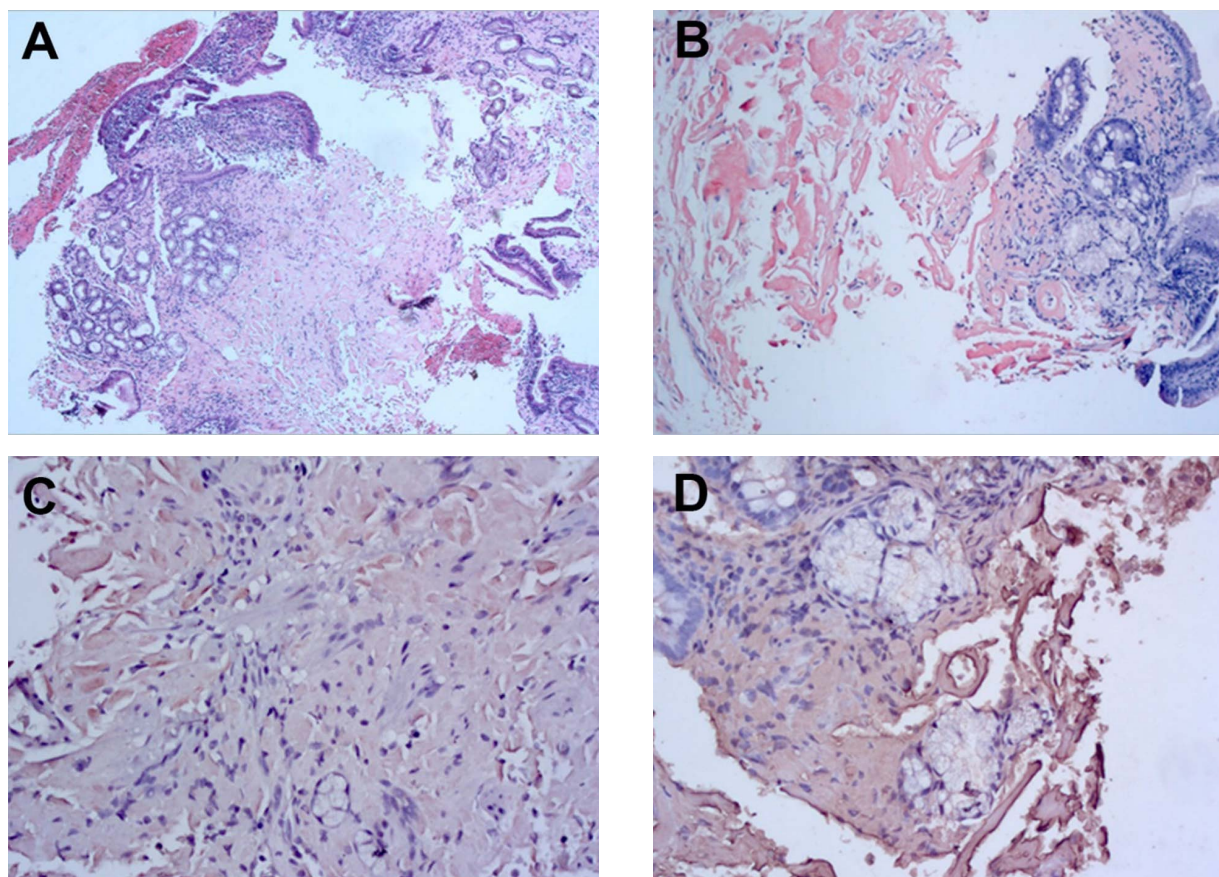


Fig. 4. Histopathological study of polypous proliferation of the duodenal mucosa of the patient U. (A) Hematoxylin-eosin staining, original magnification 50x; signs of chronic duodenitis; fragment of a glandular polyp; sharp uneven thickening in the lamina propria due to the deposition of homogeneous eosinophilic masses, areas of sclerosis. (B) Congo-red staining, original magnification 100x; positive brick red masses in the stroma, lamina propria, and walls of vessels of various sizes. (C) Immunohistochemistry of AA amyloid, original magnification 200x; AA amyloid negative expression in the stroma, lamina propria, blood vessel walls, single positive cells. (D) Immunohistochemistry of κ -light chains, original magnification 200x; κ -light chains positive expression in the stroma, lamina propria (the areas of homogeneous masses deposition), and blood vessel walls

Рис. 4. Гистопатологическое исследование полипозной пролиферации слизистой оболочки двенадцатиперстной кишки пациента У. (А) Окраска гематоксилин-эозином, исходное увеличение 50x; признаки хронического дуоденита; фрагмент железистого полипа; резкое неравномерное утолщение собственной пластинки за счет отложения однородных эозинофильных масс, участки склероза. (В) Окраска конго красным, исходное увеличение 100x; окрашенные кирпично-красные массы в строме, собственной пластинке и стенках сосудов различных размеров. (С) Иммуногистохимическое исследование АА-амилоида, исходное увеличение 200x; отсутствие экспрессии АА-амилоида в строме, собственной пластинке, стенках кровеносных сосудов, единичные клетки с экспрессией. (D) Иммуногистохимическое исследование κ -легких цепей, исходное увеличение 200x; наличие экспрессии κ -легких цепей в строме, собственной пластинке (области отложения гомогенных масс) и стенках кровеносных сосудов

of various sizes (C). Upon immunohistochemistry, phenotyping of amyloid was carried out: AA amyloid was found in uneven, focal, and mild positive expression in the stroma, blood vessel walls, and in the area of connective tissue proliferation; κ - and λ -light chains was found in diffuse positive expression in the stroma, blood vessel walls, in the areas of connective tissue proliferation and homogeneous masses deposition (D, E).

Pathomorphological diagnosis: results of pathomorphological, histochemical, and immunohistochemical studies indicate liver AL amyloidosis with

dominating λ - and κ -light chains expression, mild focal AA amyloid expression. There are signs of chronic hepatitis with mild manifestations and marked chronic changes; the Knodell histology activity index — 8; the Knodell fibrosis — 3, METAVIR — 3.

No significant impairments were found in other organs and systems.

On the basis of the revealed changes [8, 12–14], the patient presented with the following diagnosis.

Main: Primary amyloidosis involving heart, stomach, intestines, and liver. Stage 1.

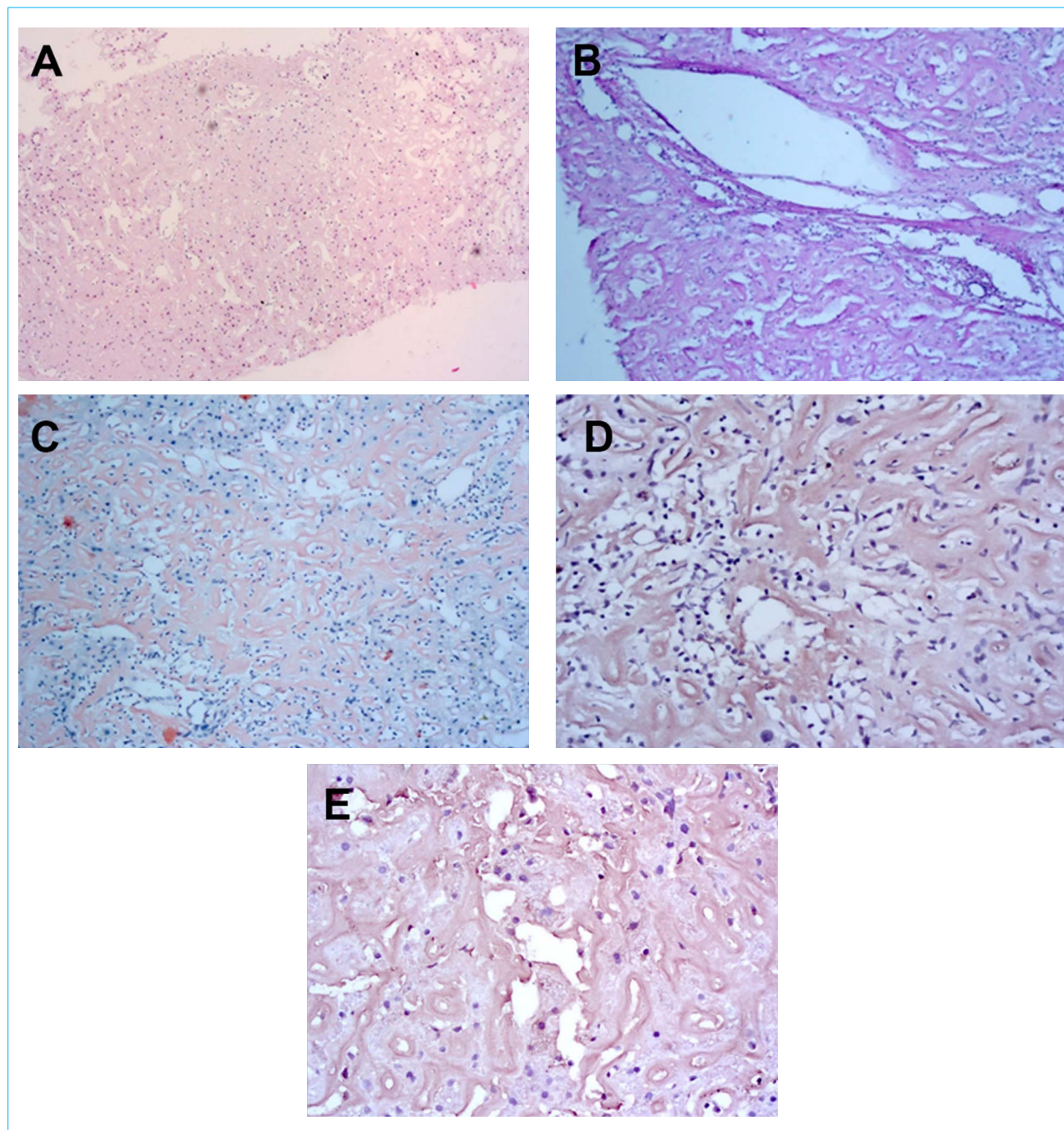


Fig. 5. Histopathological study of liver trephine biopsy of the patient. (A) Hematoxylin-eosin staining, original magnification 50x; liver trephine biopsy revealed signs of the architectonics disorder due to the marked diffuse deposition of homogeneous eosinophilic masses in the stroma, severe atrophy and degeneration of hepatocytes. (B) Periodic acid–Schiff staining, original magnification 200x; uneven marked dilatation of the portal tracts, mild focal lymphohistiocytic infiltrate along the portal tracts; perivascular and periductal fibrosis; bile ducts atrophy; vascular sclerosis. (C) Congo-red staining, original magnification 100x; positive brick-red masses in the stroma and walls of vessels of various sizes. (D) Immunohistochemistry for κ -light chains, original magnification 200x; κ -light chains diffuse positive expression in the stroma, blood vessel walls, area of connective tissue proliferation and homogeneous masses deposition. (E) Immunohistochemistry for λ -light chains, original magnification 200x; λ -light chains diffuse positive expression in the stroma, blood vessel walls, in the areas of connective tissue proliferation and homogeneous masses deposition.

Рис. 5. Гистопатологическое исследование трепан-биоптата печени пациента. (А) Окраска гематоксилин-эозином, исходное увеличение 50x; трепан-биопсия печени выявила признаки нарушения архитектоники за счет выраженного диффузного отложения однородных эозинофильных масс в строме, тяжелой атрофии и дегенерации гепатоцитов. (В) Окраска Шифф-йодной кислотой, исходное увеличение 200x; неравномерное

выраженное расширение портальных трактов, умеренный очаговый лимфогистиоцитарный инфильтрат вдоль портальных трактов; периваскулярный и перидуктальный фиброз; атрофия желчных протоков; склероз сосудов. (С) Окраска конго красным, исходное увеличение 100×; окрашенные кирпично-красные массы в строме и стенках сосудов различных размеров. (D) Иммуногистохимическое исследование к-легких цепей, исходное увеличение 200×; диффузная экспрессия к-легких цепей в строме, стенках кровеносных сосудов, области пролиферации соединительной ткани, в областях пролиферации соединительной ткани и отложения гомогенных масс. (Е) Иммуногистохимическое исследование λ-легких цепей, исходное увеличение 200×; диффузная экспрессия λ-легких цепей в строме, стенках кровеносных сосудов, в областях пролиферации соединительной ткани и отложения гомогенных масс

Concomitant: Chronic acalculous cholecystitis exacerbation. Exacerbation of chronic pancreatitis with impaired secretory function. Duodenal ulcer remission. Mild secondary anemia of chronic disease. Hypertensive heart disease, grade II, grade 2, risk 3. Heart failure, class I.

According to existing recommendations, we administered melphalan (0.22 mg/kg/day) and dexamethasone (40 mg/day) during 5 days [8, 15]. No adverse reactions were recorded. The tolerability was assessed as good, thereby the patient was recommended to continue the administered therapy on Day 1–5 of the 30-day cycle. The patient received concomitant therapy – antihypertensive, detoxification, cardio-, hepato-, and gastroprotective treatment, iron supplements. Patient's general condition improved during treatment, cardiac and gastrointestinal symptoms disappeared, and the laboratory indicators became normal. In particular, inflammatory markers normalized, NT-proBNP, rheumatoid factor, GGT, and ALP levels decreased. The patient undergoes treatment and follow-up at the clinic.

Discussion

The peculiarity of the present clinical case is the absence of renal involvement and significant heart involvement in a rather severe general condition of the patient, which is mainly caused by involvement of the liver and gastrointestinal tract with marked laboratory signs (serum GGT and ALP levels).

Therefore, guided by modern recommendations [8] with an appropriate assessment of the prognosis, we assessed the stage of the disease as stage I.

However, it should be noted that this stratification system does not take into account involvement of either the gastrointestinal tract or the liver. At the same time, some authors mention the adverse effect of gastrointestinal involvement on the overall prognosis in amyloidosis [17].

Mayo Clinic experts identified the 3 “pillars” for survival improvement of patients with systemic AL amyloidosis. The first is early disease recognition due to timely biopsy of the involved organs. The second is inhibition of plasma cell clone proliferation, reduction of cytotoxic immunoglobulin light chains production and target organs failure due to high-dose chemotherapy (daratumumab, cyclophosphamide, bortezomib, dexamethasone, melphalan), and autologous stem cell transplantation. The third “pillar” is supportive care [8].

Therapy with Melphalan plus Dexamethasone remained the standard of care in this group of patients for many years [8, 15]. The alkylating agent Cyclophosphamide may be offered as an alternative to Melphalan. Recent studies consider the proteasome inhibitor Bortezomib as monotherapy or in combination with Dexamethasone and/or Melphalan [8, 9, 14, 15]. Anti-CD38 monoclonal antibody Daratumumab in combination with Dexamethasone and/or Bortezomib can be used [8, 9, 14, 15]. The potential use of transthyretin antagonists Inotersen, Patisiran, Tafamidis, which had a certain positive effect in amyloid neuropathy, is being discussed [12]. Research on stem cell transplantation in patients with primary amyloidosis is ongoing [5]. Undoubtedly, concomitant organ-protective treatment preserves its prognostic value [5, 16].

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