Rev. Fac. Med. Hum. 2024; 24(2):172-179.
DOI: 10.25176/RFMH.v24i2.6534
CLINICAL CASE

ISSN Versión Online: 2308-0531
Facultad de Medicina Humana URP
RFMH

REPORT OF A CASE OF SYSTEMIC AL AMYLOIDOSIS IN A 65-YEAR-OLD MAN WITH CHRONIC DIARRHEA AND HEMOLACRIA

REPORTE DE UN CASO DE AMILOIDOSIS SISTÉMICA AL EN UN VARÓN DE 65 AÑOS CON DIARREA CRÓNICA Y HEMOLACRIA

Eloy Manerinc Peña Monge [1,3,a,c], Katherin Estefania Ponte Fernandez [1,a], Sonia Indacochea Cáceda [1,3,a,c], José Somocurcio Peralta [2,4,b,]

CLINICAL CASE

ABSTRACT

The case of a 65-year-old male with chronic diarrhea, periorbital ecchymosis, and hemolacria is described. Laboratory studies, biopsy, and immunohistochemical analysis were performed to confirm the diagnosis. The dependent variable was the confirmed diagnosis of AL amyloidosis, while the independent variables included clinical symptoms and diagnostic test results. Descriptive techniques were used to analyze the clinical and laboratory data. The patient presented with chronic diarrhea unresponsive to conventional treatment, periorbital ecchymosis, and hemolacria. Diagnostic studies revealed amyloid deposits in the tissues. Immunohistochemical analysis confirmed systemic light chain AL amyloidosis. Specific treatment was initiated, partially improving the symptoms and stabilizing the patient's condition. Systemic AL amyloidosis requires a high index of clinical suspicion for timely diagnosis. The combination of diagnostic studies and early treatment can improve the prognosis of these patients.

Keywords: Immunoglobulin Light-chain Amyloidosis; Diarrhea; Eye Hemorrhage. (Source: MESH-NLM)

RESUMEN

Se describe el caso de un varón de 65 años con diarrea crónica, equimosis palpebral y hemolacria. Se realizaron estudios de laboratorio, biopsia y análisis inmunohistoquímico para confirmar el diagnóstico. La variable dependiente fue el diagnóstico confirmado de amiloidosis AL, mientras que las variables independientes incluyeron los síntomas clínicos y los resultados de las pruebas diagnósticas. Se emplearon técnicas descriptivas para analizar los datos clínicos y de laboratorio. El paciente presentó diarrea crónica sin respuesta al tratamiento convencional, equimosis palpebral y hemolacria. Los estudios diagnósticos revelaron depósitos de amiloide en los tejidos. El análisis inmunohistoquímico confirmó amiloidosis sistémica de cadenas ligeras tipo AL. Se inició tratamiento específico, mejorando parcialmente los síntomas y estabilizando la condición del paciente. La amiloidosis sistémica de tipo AL requiere un alto índice de sospecha clínica para su diagnóstico oportuno. La combinación de estudios diagnósticos y tratamiento precoz puede mejorar el pronóstico de estos pacientes.

Palabras clave: Amiloidosis de Cadenas Ligeras de las Inmunoglobulinas; Diarrea; Hemorragia Ocular. (Fuente: DeCS- BIREME)

[1] Department of Internal Medicine, Hospital Nacional Edgardo Rebagliati Martins, EsSalud. Lima, Peru.
[2] Department of Pathological Anatomy, Hospital Nacional Edgardo Rebagliati Martins, EsSalud. Lima, Peru.
[3] Faculty of Human Medicine, Universidad Ricardo Palma. Lima, Peru.
[4] Faculty of Human Medicine, Universidad Nacional Mayor de San Marcos. Lima, Peru.
[a] Internist.
[b] Clinical pathologist.
[c] Professor.

Cite as: Peña Monge EM, Ponte Fernandez KE, Indacochea Cáceda S, Somocurcio Peralta J. Report of a case of systemic AL amyloidosis in a 65-year-old man with chronic diarrhea and hemolacria. Rev Fac Med Hum. 2024;24(2):172-179. doi 10.25176/RFMH.v24i2.6534

Journal home page: http://revistas.urp.edu.pe/index.php/RFMH

INTRODUCTION

Systemic AL amyloidosis is characterized by the production of abnormal immunoglobulin light chains by plasma cells. These proteins, known as amyloid, misfold and deposit in tissues, primarily affecting the heart, kidneys, liver, and peripheral nervous system. It is a rare disease with an incidence of approximately eight people per million per year, but its morbidity and mortality are high[1]. The average age at diagnosis is 64 years, and 25% of patients die within the first six months [2]. Diagnostic delays are common and have detrimental consequences for prognosis, making timely recognition of the disease critically important.

The clinical manifestations of AL amyloidosis are varied and can include chronic diarrhea, dermal and periorbital bruising (raccoon eyes), and hemolacria, a rare sign characterized by blood discharge through the lacrimal punctum. These symptoms are often nonspecific, contributing to diagnostic delays. Chronic diarrhea may result from amyloid infiltration in the gastrointestinal tract, while cutaneous manifestations and hemolacria result from vascular fragility induced by amyloid deposits [3].

In the suspicion of systemic amyloidosis, one of the first-line detection tools for cardiac involvement is echocardiography. The most important predictive echocardiographic feature, though not specific, is left ventricular hypertrophy. Amyloid deposits produce a hyperreflective appearance that, in 2D images, gives a speckled appearance to the myocardium (granular sparkling texture).

The definitive diagnosis of AL amyloidosis and its classification are based on the histological demonstration of amyloid deposits and immunohistochemical typing. However, in the early stages, patients have scant amyloid deposits, significantly reducing the sensitivity of Congo red staining. Therefore, combining a skin fat biopsy with a rectal mucosa biopsy is recommended to increase diagnostic sensitivity; a negative result in both biopsies makes the diagnosis highly unlikely [4]. The treatment goal is to achieve a complete hematological response to prevent the progression of organ damage. Therapeutic options include bone marrow transplantation and, for ineligible patients, chemotherapy consisting of dexamethasone, cyclophosphamide, bortezomib, and an anti-CD38 monoclonal antibody (daratumumab). These therapies have shown variable response and survival rates, underscoring the need for personalized treatment based on the individual characteristics of the patient and the stage of the disease [5].

The following case report presents a patient with initial symptoms of chronic diarrhea accompanied by raccoon eyes and hemolacria, illustrating the diagnostic and therapeutic challenges of this disease.

CASE REPORT

We present the case of a 63-year-old male patient, originally from Huaraz and residing in Lima, with a clinical history of hypertension for 30 years. The patient presented with a year-long history of watery bowel movements two to three times a day and a weight loss of 30 kg. He sought medical consultation with Gastroenterology, where endoscopy and colonoscopy studies were inconclusive. A week before his hospitalization, the patient experienced an increase in bowel movement frequency to three to four times a day, followed by an episode of syncope.

On physical examination, the patient was alert, lucid, and oriented. Bruising was observed in the anterior thoracic region approximately 3 x 3 cm, chest and lungs without alterations, regular cardiac rhythm with isolated extrasystoles, soft and depressible abdomen, non-tender, and mild to moderate edema in the lower limbs. Serum levels of hemoglobin, urea, creatinine, and glucose were within the reference range, while total proteins were decreased at 3.8 g/dL (range 6-8 g/dL). Urine examination showed severe proteinuria (+++/+++). The electrocardiogram revealed signs of left ventricular hypertrophy without ST segment changes. During his hospitalization, the patient presented with hemolacria and periorbital bruising (Figures 1 and 2).

Figure 1. Hemolacria in a patient with systemic AL amyloidosis.

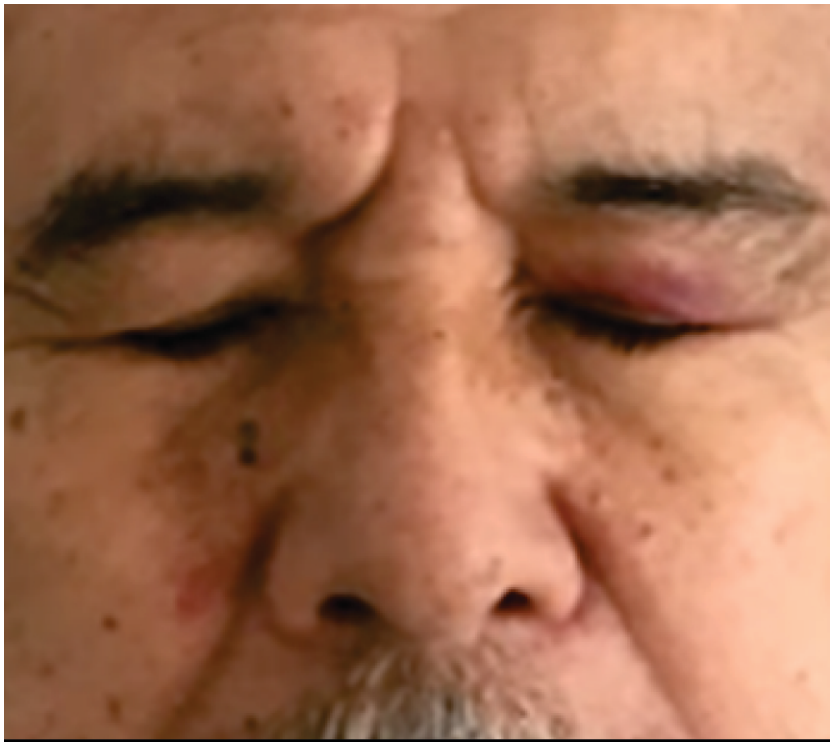


Figure 2. Left eyelid ecchymosis in a patient with systemic AL amyloidosis.

The coagulation profile showed a prolonged thromboplastin time of 60 seconds (range 25-35 seconds) with a deficiency of factor X. The 24-hour proteinuria was 900 mg/24 h. The urine electrophoretic proteinogram showed kappa/lambda light chains in a ratio of 0.81 (Table 1). Transthoracic echocardiography reported concentric hypertrophy of the left ventricle with a ground-glass appearance (Figure 3). Bone marrow biopsy showed 10% plasma cells. Given the probable case of systemic amyloidosis, biopsies of the colon, kidney, and subcutaneous connective tissue were performed; all were positive for Congo red staining, confirming the presence of amyloid deposits, with AL-type immunohistochemistry (Figure 4).

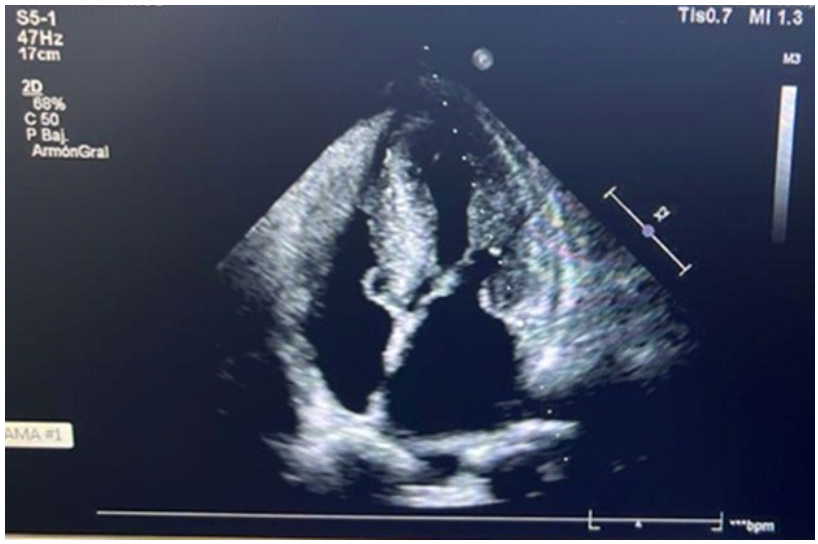
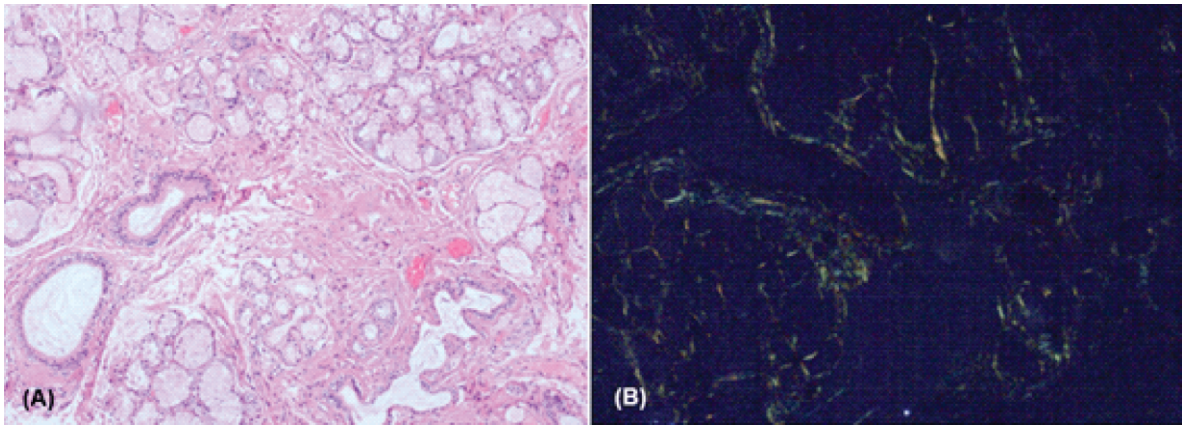


Figure 3. Transthoracic echocardiogram showing concentric hypertrophy of the left ventricle with a ground-glass appearance.



A. Microscopic image of salivary gland with Hematoxylin-Eosin at 10x magnification. Shows an increase in interstitial connective tissue with mild vascular thickening and periductal basement membrane thickening. **B.** Microscopic image with Congo Red under polarized light microscopy of salivary gland at 20x magnification. Highlights the structure of the salivary gland, showing positivity for amyloid material at the interstitial, vascular, and periductal levels.

Figure 4. Microscopic images of connective tissue with amyloid deposits in a patient with systemic AL amyloidosis.

Table 1. Laboratory and pathological analysis.

Laboratory Analysis	
Hemoglobin / Leukocytes / Platelets	
Prothrombin Time (PT)	1 311 (62.2%)
Thromboplastin Time (APTT)	798 (37.8%)
APTT Mixing Test	
Factor X	269 (12.8%)
Glucose / Creatinine / Urea	646 (30.6%)
Sodium / Potassium / Chlorine	494 (23.4%)
Calcium / Phosphorus / Magnesium	424 (20.1%)
AST (SGOT) / ALT (SGPT) / Alkaline Phosphatase	276 (13.1%)
Albumin / Globulin	
Coproparasitological, Coprofunctional,	936 (44.4%)
Culture for Common Germs, Fungi, and KB	98 (4.7%)
Urine examination	1075 (50.9%)
24-hour Urine proteins	
Serum Light Chains	126 (5.9%)
(kappa/lambda)	1983 (94.0%)
Urine Light Chains (kappa/lambda)	
Pathological Analysis	
Renal Biopsy	Focal and segmental glomerulosclerosis, collapsing variant. Congo red: positive for amyloid tissue.
Rectal Mucosa Biopsy	Rectal mucosa with preserved glandular architecture, focal significant intraepithelial lymphocytosis, and apoptosis. Congo red: positive for amyloid tissue.
Subcutaneous Connective Tissue Biopsy	Fragment of skin and adipose tissue with areas of hemorrhage, arterial vessels with wall thickening. Congo red: positive for amyloid tissue.
Bone Marrow Biopsy	10-30% cellularity, presence of mature elements of all three lineages, no evidence of malignant neoplasia. IHC: 10% plasma cells, most expressing Lambda chain.

PT: Prothrombin Time.
APTT: Activated Partial Thromboplastin Time.
AST: Aspartate Aminotransferase.
ALT: Alanine Aminotransferase.
NV: Normal Values.
KB: Koch's Bacilli.
IHQ: Immunohistochemistry.

The diagnosis was conclusive for systemic AL amyloidosis with renal, cardiac, and gastrointestinal involvement. He received systemic chemotherapy with cyclophosphamide, dexamethasone, thalidomide, and bortezomib. After the first infusion of bortezomib, he developed atrial fibrillation and decompensated heart failure, leading to a change to an alternative regimen with lenalidomide, cyclophosphamide, and dexamethasone. Two months later, the patient passed away.

DISCUSSION

Amyloidosis has 22 different types of localized forms and 18 types of systemic forms. The most common systemic forms are light-chain amyloidosis (AL) and transthyretin amyloidosis (ATTR). Systemic AL amyloidosis, also known as primary or light-chain amyloidosis, is characterized by the production of abnormal immunoglobulin light chains by CD38+ plasma cells in the bone marrow.

These proteins misfold and deposit in tissues as amyloid. It is a rare and complex disease associated with high morbidity and mortality. It affects approximately eight people per million, with a mean age at diagnosis of 64 years. Advanced age is the main risk factor, and 25% of patients with light-chain amyloidosis die within six months of diagnosis [6-9]. A review of the literature found no reported cases of hemolacria in patients with amyloidosis in Peru, Latin America, or worldwide. Only a few cases or images of hemolacria related to other pathologies have been found. Diagnostic delays are common and have detrimental consequences for patient prognosis. Therefore, clinical suspicion and the use of biomarkers and imaging technologies are vital for timely diagnosis.

Systemic amyloidosis should be considered in the differential diagnosis of adult non-diabetic nephrotic syndrome. Additionally, the collapsing form is the most aggressive presentation of this type of glomerulopathy, and the severe form is associated with viral infectious processes such as HIV, CMV, and HBV, which were ruled out in this case. Other clinical manifestations include heart failure with preserved ejection fraction, particularly if restrictive features are present; unexplained hepatomegaly without imaging abnormalities; peripheral neuropathy with distal sensory symptoms such as paresthesias and dysesthesias (though autonomic manifestations may occasionally be the presenting feature); and monoclonal gammopathy of undetermined significance with atypical clinical features [7]. This list of clinical features should also include chronic diarrhea, cutaneous manifestations such as periorbital bruising (raccoon eyes), dermal bruising, macroglossia, and, as in our case, hemolacria.

This case report illustrates a case of systemic AL amyloidosis that began with chronic diarrhea. Despite repeated medical consultations and multiple endoscopic and colonoscopic studies, no timely diagnosis was made. Chronic diarrhea is one of the nonspecific and frequent symptoms of the disease, occurring in 40-60% of cases due to amyloid infiltration at the neuromuscular and mucosal levels of the gastrointestinal tract, often causing motility disturbances, resulting in diarrheal or subocclusive episodes. Hemorrhagic episodes due to mucosal infiltration and macroglossia occur in up to 50% of cases [10]. During the course of hospitalization, ecchymotic dermal lesions were identified in the anterior thoracic and periorbital regions. Subsequently, the patient presented with bloody tears, a rare clinical sign known as hemolacria.

This sign is produced by the accumulation of amyloid fibrils that increase vascular fragility. Additionally, factor X binds to amyloid fibrils, mainly in the liver and spleen, causing a deficiency of this factor. The most clinically significant coagulopathy in amyloidosis is factor X deficiency, the most frequent cause of bleeding. The incidence of acquired factor X deficiency associated with systemic AL amyloidosis ranges from 8.7% to 14% [11,12]. There are no records of the incidence of hemolacria in patients with amyloidosis.

With clinical suspicion of systemic deposition disease, an echocardiogram was requested, revealing concentric left ventricular hypertrophy with a ground-glass appearance. Echocardiography is the cornerstone of non-invasive imaging for cardiac amyloidosis, as well as a first-line detection tool. The most important predictive echocardiographic feature, though not specific, is left ventricular hypertrophy, mainly in the interventricular septum. Amyloid deposits produce a hyperreflective appearance; 2D images give a speckled appearance to the myocardium (granular sparkling texture), most commonly in the ventricular septum or posterior wall, while the apex does not show this sign[13].

Diagnosis and classification are based on the histological demonstration of amyloid deposits. Biopsies of affected organs, such as the kidney or heart, have high sensitivity; however, these invasive procedures can carry significant risks, such as bleeding and arrhythmia.

Abdominal subcutaneous fat, rectal, skin, salivary gland, and bone marrow biopsies are frequently used to detect amyloid deposits in patients with symptoms of the disease. However, the sensitivity values of these approaches vary considerably. Abdominal subcutaneous fat biopsy is a safe, simple, and low-cost method, with a sensitivity of 67% to 93%, but patients in the early stages of amyloidosis have scant amyloid deposits, significantly reducing the sensitivity of Congo red staining. Rectal biopsy has a sensitivity of 75% to 80%. Gertz et al.[7] reported that combining abdominal fat biopsy with bone marrow biopsy results in an 85% detection rate for diagnosis. Combining skin fat biopsy with rectal mucosa biopsy can identify amyloid deposits in nearly all patients, and a negative result from both biopsies makes the diagnosis highly unlikely[14]. In this case, abdominal fat and rectal mucosa biopsies were performed, with Congo red staining yielding positive results, and immunohistochemistry, the current standard for determining the type of amyloid, typed it as AL.

The treatment goal for AL amyloidosis is to achieve a complete hematological response to halt the progression of organ damage. The first line of therapy is considered to be bone marrow transplantation. For ineligible patients, chemotherapy is proposed, consisting of dexamethasone, cyclophosphamide, bortezomib, and an anti-CD38 monoclonal antibody (daratumumab). This combination has shown a high complete hematological response rate and was approved by the Food and Drug Administration (FDA) in 2021. However, the limitation of this treatment in patients with advanced heart failure or renal damage should be considered [15].

CLINICAL CASE

Authorship contribution: PME and PFK contributed to the idea, data collection, analysis, and manuscript preparation; ICS contributed to the analysis, preparation, and revision of the manuscript; SPJ contributed to the reading and review of pathology slides and manuscript revision.

Funding: Self-funded.

Correspondence: *Eloy Manerinc Peña Monge.*
Address: *Av. Edgardo Rebagliati 490, Jesús María 15072.*
Telephone: *01 2654901*
Email: ***eloypena@example.com***

Conflict of interest: The authors declare no conflicts of interest.

Received: March 15, 2024.
Approved: April 29, 2024.

REFERENCES

1. Kumar N, Zhang NJ, Cherepanov D, Romanus D, Hughes M, Faller DV. Global epidemiology of amyloid light-chain amyloidosis. Orphanet J Rare Dis. 2022;17(1):278. doi:10.1186/s13023-022-02414-6

2. Baker KR. Light Chain Amyloidosis: Epidemiology, Staging, and Prognostication. Methodist Debakey Cardiovasc J. 18(2):27–35. doi:10.14797/mdcvj.1070

3. Elsayed M, Usher S, Habib MH, Ahmed N, Ali J, Begemann M, et al. Current Updates on the Management of AL Amyloidosis. J Hematol. 2021;10(4):147–61. doi:10.14740/jh866

4. Picken MM. The Pathology of Amyloidosis in Classification: A Review. Acta Haematol. 2020;143(4):322–34. doi:10.1159/000506696

5. Bal S, Landau H. AL amyloidosis: untangling new therapies. Hematology Am Soc Hematol Educ Program. 2021;2021(1):682–8. doi:10.1182/hematology.2021000305

6. Zanwar S, Gertz MA, Muchtar E. Immunoglobulin Light Chain Amyloidosis: Diagnosis and Risk Assessment. J Natl Compr Canc Netw. 2023;21(1):83-90. doi:10.6004/jnccn.2022.7077

7. Gertz MA, Dispenzieri A. Reconocimiento, pronóstico y tratamiento de la amiloidosis sistémica: una revisión sistemática. JAMA. 2020;324(1):79–89. doi:10.1001/jama.2020.5493

8. McCausland KL, White MK, Guthrie SD, et al. Light Chain (AL) Amyloidosis: The Journey to Diagnosis. Patient. 2018;11(3):207–216. doi:10.1007/s40271-017-0273-5

9. Stelmach-Gołdyś A, Zaborek-Łyczba M, Łyczba J, Garus B, Pasiarski M, Mertowska P, et al. Physiology, Diagnosis and Treatment of Cardiac Light Chain Amyloidosis. J Clin Med. 2022;11(4):911. doi:10.3390/jcm11040911

10. Dahiya DS, Kichloo A, Singh J, Albosta M, Wani F. Gastrointestinal amyloidosis: A focused review. World J Gastrointest Endosc. 2021;13(1):1-12. doi:10.4253/wjge.v13.i1.1

11. Nicol M, Siguret V, Vergaro G, Aimo A, Emdin M, Dillinger JG, et al. Thromboembolism and bleeding in systemic amyloidosis: a review. ESC Heart Failure. 2022;9(1):11–20. doi:10.1002/ehf2.13701

12. Thompson CA, Kyle R, Gertz M, Heit J, Pruthi R, Pardanani A. Systemic AL amyloidosis with acquired factor X deficiency: a study of perioperative bleeding risk and treatment outcomes in 60 patients. Am J Hematol. 2010;85(3):171–173. doi:10.1002%2Fajh.21603

13. Di Nunzio D, Recupero A, de Gregorio C, Zito C, Carerj S, Di Bella G. Echocardiographic findings in cardiac amyloidosis: inside two-dimensional, Doppler, and strain imaging. Curr Cardiol Rep. 2019;21(2):7. doi:10.1007/s11886-019-1094-z

14. Li T, Huang X, Cheng S, et al. Utility of abdominal skin plus subcutaneous fat and rectal mucosal biopsy in the diagnosis of AL amyloidosis with renal involvement. PLoS ONE. 2017;12(9). doi:10.1371/journal.pone.0185078

15. Ikura H, Endo J, Kitakata H, Moriyama H, Sano M, Fukuda K. Molecular mechanism of pathogenesis and treatment strategies for AL amyloidosis. Int J Mol Sci. 2022;23(11):6336. doi:10.3390/ijms23116336