Chapter

Renal Amyloidosis

Elena Zakharova

Abstract

Modern amyloid nomenclature, based on the amyloid fibril proteins, includes 31 types of amyloidosis. Renal involvement is commonly seen in AA, AL, and several other hereditary and acquired amyloidoses. AA amyloidosis, constituting up to 45% of all systemic amyloidosis cases, is associated with wide variety of chronic inflammatory conditions. The precursor protein of the fibrils in AA amyloidosis is an apolipoprotein, called serum amyloid A, and produced in the liver in response to proinflammatory cytokines. AL amyloidosis is actually known to be the most common form of systemic amyloidosis in the Western countries. In this type of amyloidosis the precursor proteins are monoclonal immunoglobulin light chains, produced by plasma cell clone. Clinical diagnosis of AA and AL systemic amyloidosis is based on the presence of proteinuria or nephrotic syndrome and impaired kidney function in patients with extrarenal manifestations. Kidney biopsy is crucial for the diagnostics, and while Congo red staining with examination of Congo-positive material in the polarized light is confirmative for amyloidosis as such, immune staining, helpful to distinguish AA and AL types, guides treatment strategies. In cases when neither AA nor AL amyloidosis are confirmed, one should consider rare types of amyloidosis—ALECT2, AapolA, AFib or ALys.

Keywords: light chains, serum amyloid A, nephrotic syndrome, kidney function, kidney biopsy

1. Introduction

Modern amyloid nomenclature, based on the amyloid fibril proteins, includes 31 types of amyloidosis [1]. Renal involvement is commonly seen in AL, AH, AA, ALECT2, and several other hereditary and acquired amyloidoses [1–4], main features are summarized in **Table 1**.

We describe below two most common types of amyloidosis, damaging kidneys—AA amyloidosis and AL amyloidosis.

2. AA amyloidosis

The precursor protein of the fibrils in AA amyloidosis is an apolipoprotein, called serum amyloid A, and produced in the liver in response to proinflammatory cytokines. AA amyloidosis, constituting up to 45% of all systemic amyloidosis cases, is associated with wide variety of chronic inflammatory conditions [5–7], summarized in the **Table 2**.

Protein precursor	Fibril protein	Clinical setting	Kidney damage	Other target organs
Immunoglobulin light chain	AL	"Primary" amyloidosis, LPD	70%	All organs
Immunoglobulin heavy chain	AH	LPD	—	All organs
Serum amyloid A	AA	Chronic inflammation	90%	All organs except CNS
Leucocyte chemotactic factor-2	ALECT2	Not defined as acquired or hereditary	Primarily	Liver
Transthyretin	ATTR	Hereditary and acquired	Common	Heart, Eye, PNS, ANS, ligaments, tendon synovium, leptomeninges
Apolipoprotein A I	AapoAI	Hereditary	Common	Heart, liver, PNS, testis, larynx, skin
Apolipoprotein A II	AapoAII	Hereditary	Primarily	Many organs
Apolipoprotein A IV	AapoAIV	Acquired	Primarily	—
Fibrinogen α	AFib	Hereditary	Primarily	—
Lysozyme	ALys	Hereditary	Primarily	Liver

LPD, lymphoproliferative disorders; CNS, central nervous system; PNS, peripheral nervous system; ANS, autonomous nervous system.

Table 1.
Amyloidoses with renal involvement.

Kidneys are the main site of involvement in AA amyloidosis, renal damage (**Figure 1**) occurs in 90% of cases, presenting with proteinuria, nephrotic syndrome (NS) and impaired kidney function [3, 6].

Rheumatoid arthritis, if poorly controlled, still remains one of the most common inflammatory diseases, associated with AA amyloidosis (**Figure 2**).

However, many other conditions, listed in **Table 2**, may be causative for AA amyloidosis. Frequency of the diseases, associated with AA amyloidosis in the patients, followed in our unit, is shown in **Table 3**.

Worthy to note, that beyond traditional causes, several rare conditions, such as sarcoidosis, cystic fibrosis and Castleman's disease, complicated by AA amyloidosis, might be seen in the real practice (**Figures 3** and **4**).

Moreover, we recently described a patient with sclerosing angiomatoid nodular transformation of the spleen and AA amyloidosis [8], association previously unreported (**Figures 5** and **6**).

Presence of NS or proteinuria in patients with the history of any kind of chronic inflammatory conditions, indicates a high "suspicion index' with AA amyloidosis. The diagnosis demands pathology confirmation with kidney biopsy, demonstrating not only positive Congo red staining of the material, infiltrating kidney tissue (see **Figure 1**), but also apple-green birefringence in polarized light (**Figure 7**) and serum amyloid A expression (**Figure 8**).

Treatment goal in patients with AA amyloidosis is a complete control of the inflammatory process [6]. Due to the various characters of the underlying diseases, treatment may include surgery, antibiotics, anti-TNF agents, colchicine and several novel drugs. Kidney transplantation for the patients with the end stage of renal disease (ESRD) is an important option and may be considered if a stable control of the underlying disease has been achieved.

Infectious conditions with persistent inflammation	**Chronic non-infectious diseases with persistent inflammation**
Conditions predisposing to chronic infections	*Arthritis*
• Cystic fibrosis	• Rheumatoid arthritis
• Epidermolysis bullosa	• Ankylosing spondylitis
• Paraplegia	• Adult Still disease
• Jejunoileal bypass	• Juvenile idiopathic arthritis
• Intravenous drugs use	• Psoriatic arthritis
	• Gout
Immunodeficiency's predisposing to chronic infections	*Bowel diseases*
• Common variable immunodeficiency	• Crohn's disease
• Hypogammaglobulinemia	• Ulcerative colitis
• X-linked agammaglobulinemia	*Systemic vasculitis*
• Cyclic neutropenia	• Behcet's disease
• HIV/AIDS	• Polyarteritis nodosa
• Other immunodeficiencies	• Giant cell vasculitis
	• Takayasu's arteritis
	• Polymyalgia rheumatica
Chronic infections	*Other diseases*
• Bronchiectasis	• Sarcoidosis
• Osteomyelitis	• SAPHO syndrome
• Tuberculosis	• Schnitzler syndrome
• Leprosy	• Rosai-Dorfman disease
• Chronic pyelonephritis	• Recurrent idiopathic pericarditis
• Whipple's disease	
• Chronic cutaneous ulcers	
Neoplastic diseases	**Hereditary autoinflammatory syndromes**
Blood malignancies	*Classic*
• Castleman's disease	• Familial Mediterranean fever
• Hodgkin's lymphoma	*Rare*
• Waldenstrom macroglobulinemia	• TRAPS
• Hairy cell leukemia	• Muckle-Wells syndrome
Solid tumors	• NOMID/CINCA syndrome
• Hepatic adenoma	• Hyper-IgD syndrome
• Renal cell carcinoma	• Other monogenic autoinflammatory syndromes
• Adenocarcinoma of the lung	
• Adenocarcinoma of the gut	
• Mesothelioma	

HIV, human immunodeficiency virus; AIDS, acquired immunodeficiency syndrome; SAPHO, synovitis, acne, pustules, hyperostosis, osteitis; TRAPS, TNF receptor associated periodic syndrome; NOMID, neonatal multisystem inflammatory disease; CINCA, chronic infantile neurological cutaneous and articular syndrome.

Table 2.
Diseases, associated with AA amyloidosis.

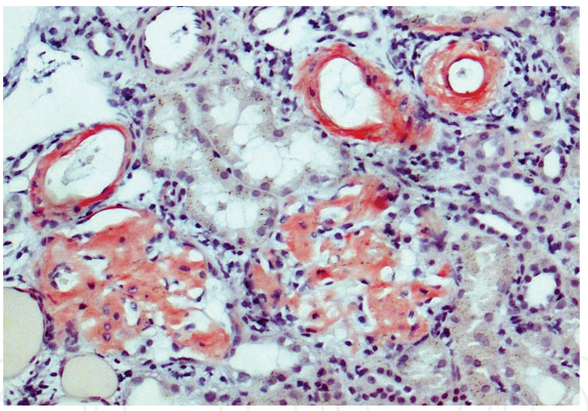

Figure 1.
Renal AA amyloidosis, Congo red 100×.

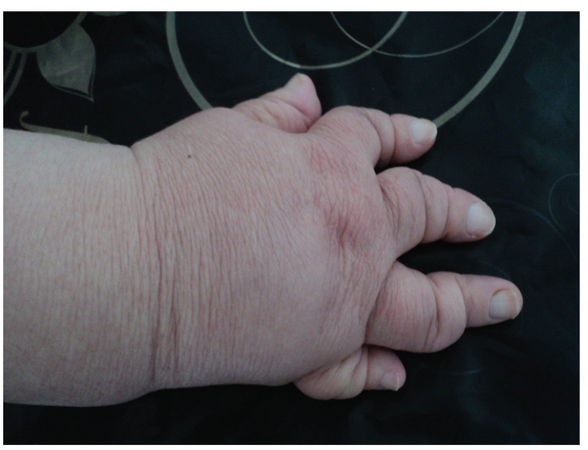

Figure 2.
Rheumatoid arthritis, complicated by renal AA amyloidosis with nephrotic syndrome.

Associated disease	Patients (N)	%
Rheumatoid arthritis	64	44.1
Ankylosing spondylitis	16	11.0
Psoriatic arthritis	7	4.8
Crohn's disease/ulcerative colitis	3	2.0
Sarcoidosis	1	0.7
Mediterranean fever	14	9.6
Hyper-IgD syndrome	1	0.7
Bronchiectasis	10	6.8
Osteomyelitis	7	4.8
Paraplegia	6	4.1
Tuberculosis	4	2.7
Chronic cutaneous ulcers	3	2.0
Cystic fibrosis	1	0.7
Lung tumors	3	2.0
Hodgkin's lymphoma	2	1.4
Castleman's disease	2	1.4
Sclerosing angiomatoid nodular transformation of the spleen	1	0.7
Total	145	100

Table 3.
Spectrum of the diseases, associated with AA amyloidosis, personal data, unpublished.

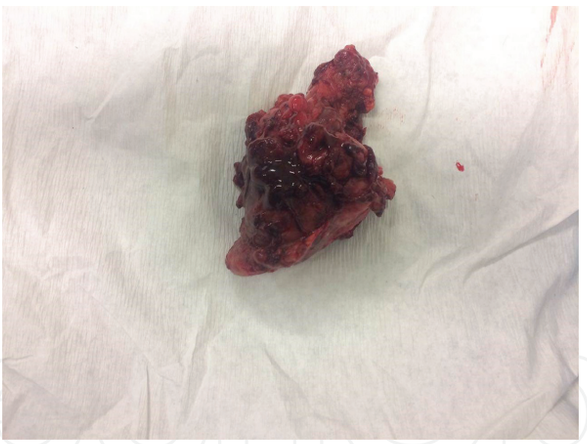

Figure 3.
Castleman's disease, unfixed gross specimen.

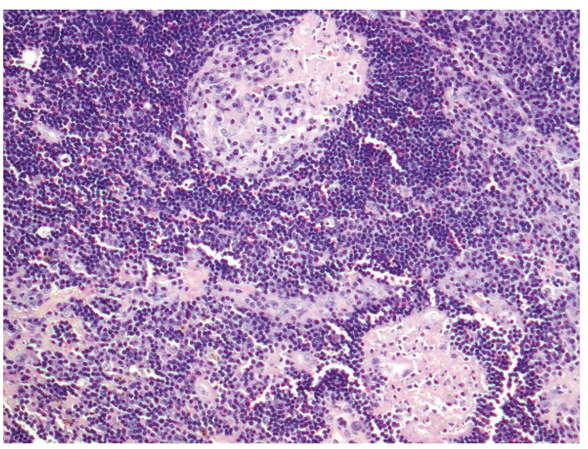

Figure 4.
Castleman's disease, atypical lymphoid tissue, hematoxylin & eosin 100×.

Figure 5.
Sclerosing angiomatoid nodular transformation of the spleen. Formalin-fixed gross specimen.

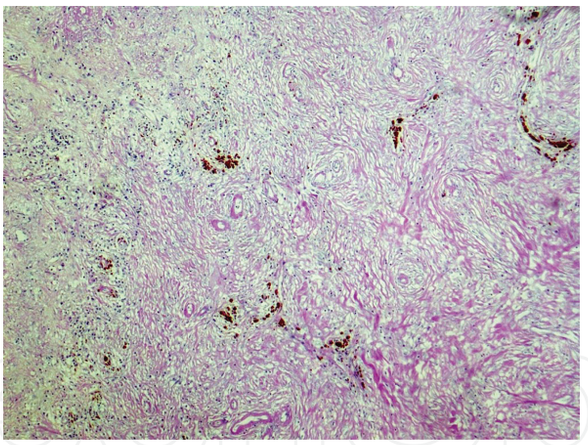

Figure 6.
Sclerosing angiomatoid nodular transformation of the spleen. PAS 100×.

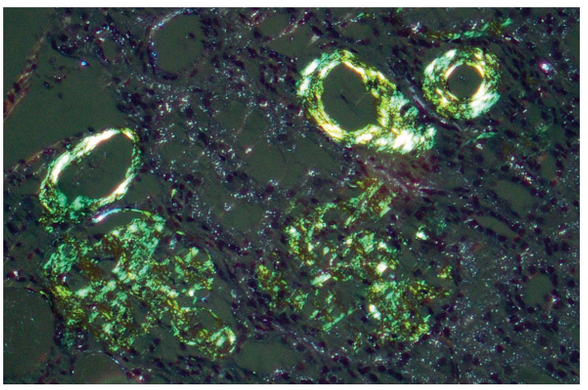

Figure 7.
Renal AA amyloidosis, Congo red 100×, polarized light.

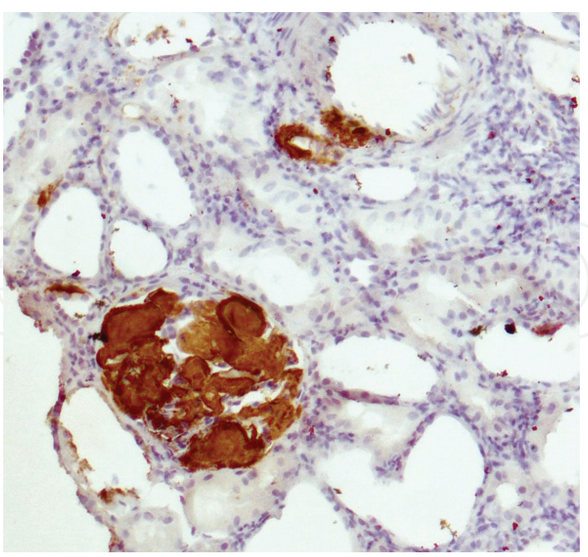

Figure 8.
Renal AA amyloidosis, serum amyloid A, immunoperoxidase 100×.

3. AL amyloidosis

The precursor proteins of the fibrils in AL amyloidosis are monoclonal immunoglobulin light chains, produced by plasma cell clone. AL amyloidosis, which is the most prevalent type of systemic amyloidosis in the Western countries, sometimes

is associated with B cell lymphoproliferative disorders—multiple myeloma, Waldenström macroglobulinemia and non-Hodgkin lymphomas [9–14]. However usually AL amyloidosis is associated with low-grade plasma cell clone and do not meet the criteria for multiple myeloma or lymphoplasmacytic lymphoma, therefore formerly it was known as "primary" [15–18].

In the real practice, among 128 patients with biopsy-proven AL amyloidosis, followed in our unit, 25 were diagnosed with multiple myeloma, 1—with Waldenström macroglobulinemia, and 102—with AL amyloidosis ("primary").

Kidneys and heart are the main sites of involvement in AL amyloidosis with the occurrence up to 70% of cases. Renal involvement typically presents with proteinuria or NS, which is manifested in more than 50% of patients at the time of diagnosis, and impaired kidney function progressing towards ESRD in about 20% of cases over time [19–21].

AL amyloidosis is diagnosed by demonstration of monoclonal deposits in the sites of amyloid deposition in the kidney (**Figures 9–11**).

Kidney biopsy is usually indicated for significant proteinuria and/or renal insufficiency in patients with signs and symptoms of heart, liver, tongue, intestine, peripheral and autonomous nervous system and soft tissues damage (**Figures 12–17**).

Monoclonal protein studies should be performed to match the monoclonal protein in circulation with the monoclonal deposits in the kidney (**Figure 18**).

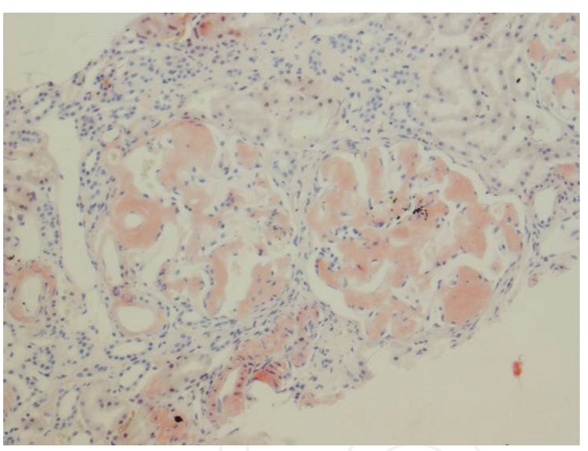

Figure 9.
Renal AL amyloidosis, Congo red 100×.

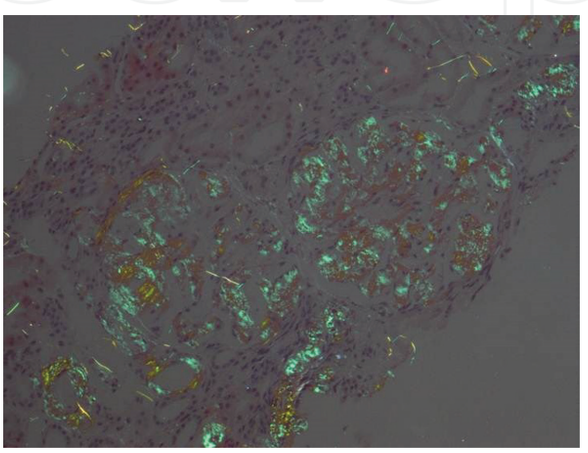

Figure 10.
Renal AL amyloidosis, Congo red 100×, polarized light.

Different treatment regimens had been used since 1997, when melphalan was introduced—melphalan and prednisone (MP), melphalan and dexamethasone (MD), and high dose melphalan with autologous stem cell transplantation (ASCT).

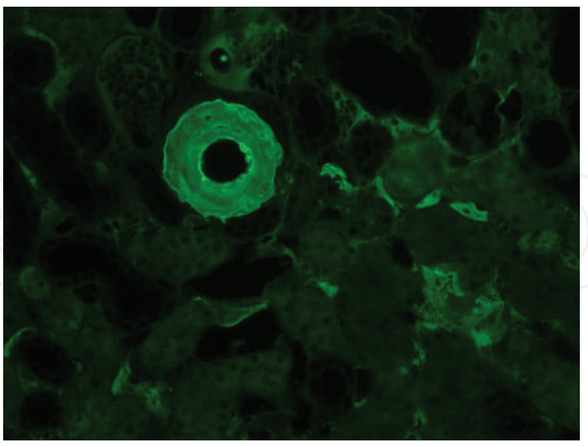

Figure 11.
Renal AL amyloidosis, light chain lambda, immunofluorescence 100×.

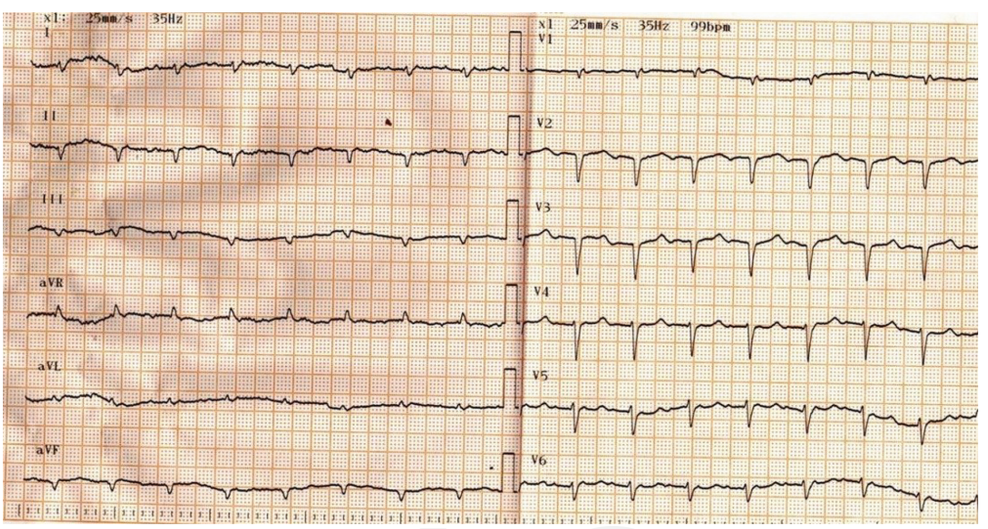

Figure 12.
AL amyloidosis, electrocardiogram, low-voltage waves in all leads.

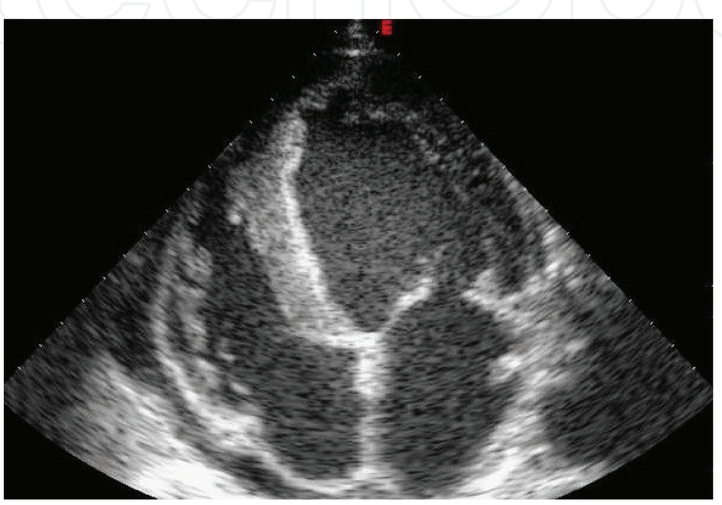

Figure 13.
AL amyloidosis, echocardiogram, myocardial mirror-like appearance.

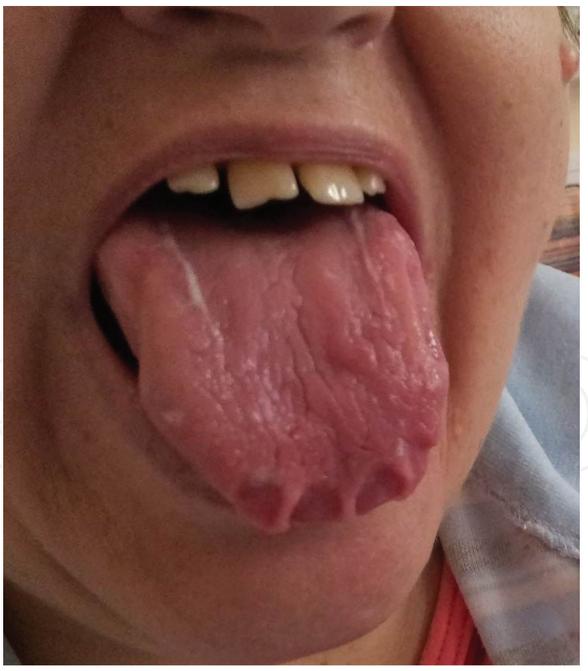

Figure 14.
AL amyloidosis, macroglossia.

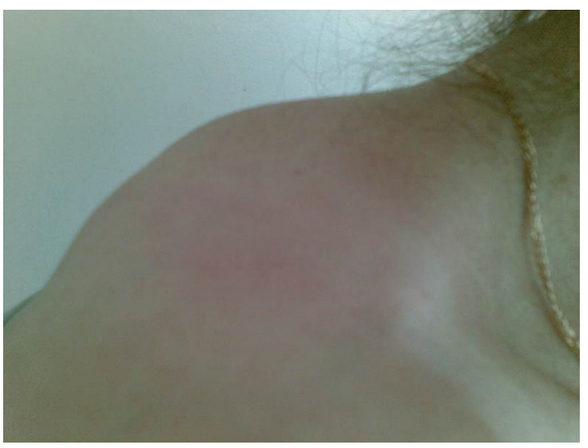

Figure 15.
AL amyloidosis, "shoulder pad" symptom.

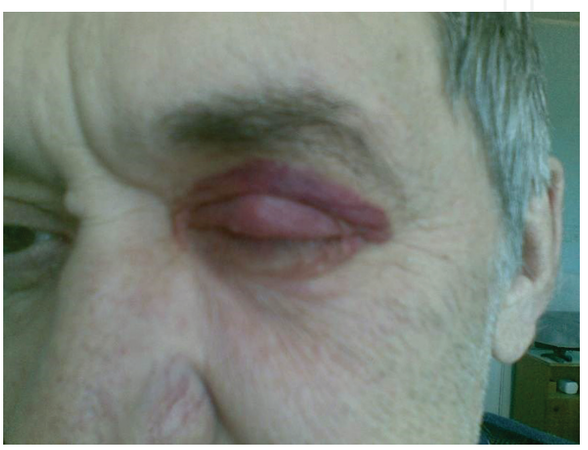

Figure 16.
AL amyloidosis, "racoon eye" symptom.

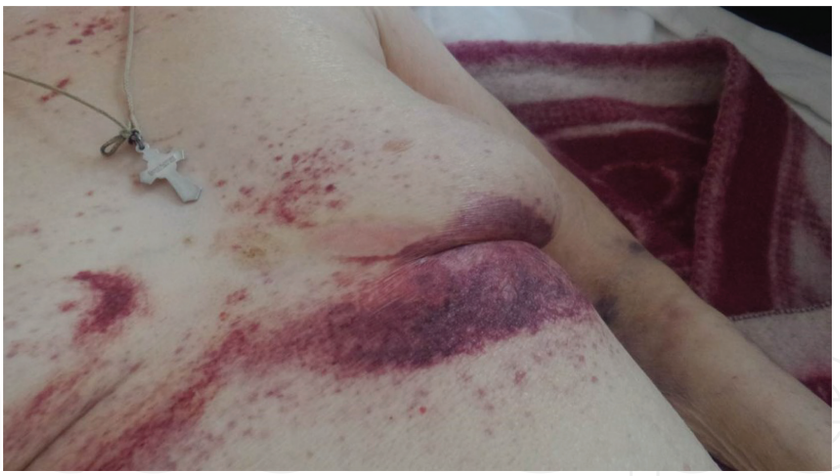

Figure 17.
AL amyloidosis, spontaneous subcutaneous hemorrhages.

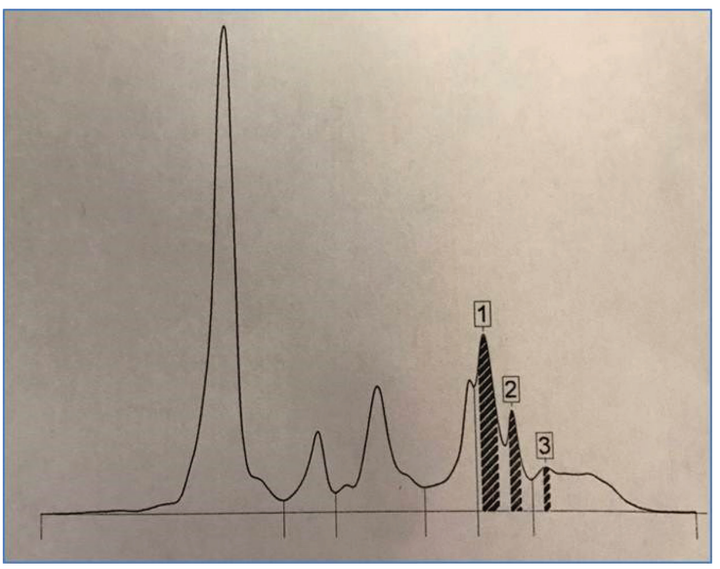

Figure 18.
Serum electrophoresis, M-spike.

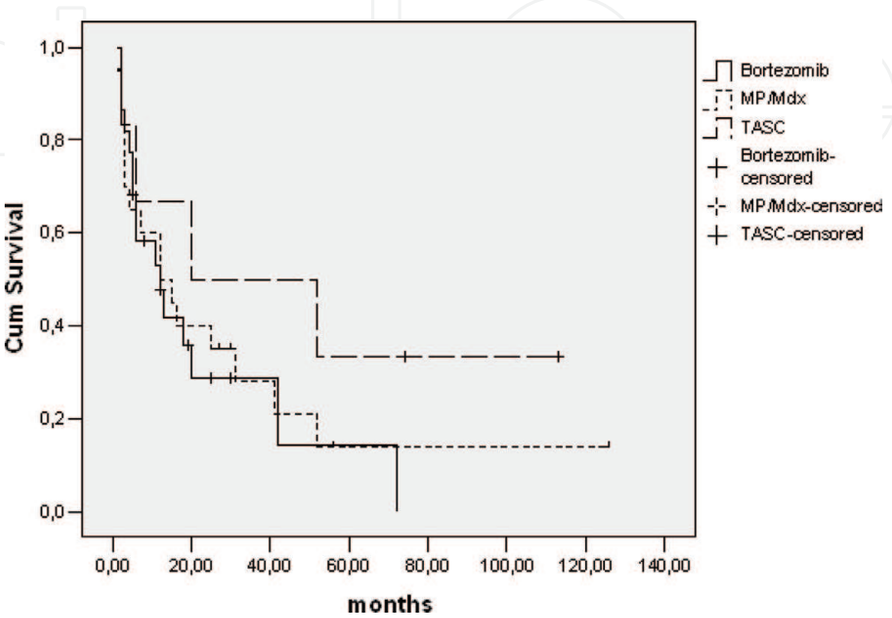

Figure 19.
Treatment results in 49 patients with AL amyloidosis, personal data [23].

Currently recommended treatment for AL amyloidosis, including cyclophosphamide-thalidomide-dexamethasone (CTD), bortezomib-dexamethasone (BD), cyclophosphamide-bortezomib-dexamethasone(CBD) regimens with relatively fast hematological response were adopted from multiple myeloma treatment protocols [22]. In our experience of treatment of systemic "primary" AL amyloidosis with kidney involvement using different regimens over almost three decades, cumulative survival did not differ statistically between melphalan-based and bortezomib-based regimens (**Figure 19**) [23].

4. Conclusions

Clinical diagnosis of AA and AL systemic amyloidosis, most often affecting kidneys, is based on the presence of proteinuria or nephrotic syndrome and impaired kidney function in patients with extrarenal manifestations. Kidney biopsy is crucial for the diagnostics, and while Congo red staining with examination of Congo-positive material in the polarized light is confirmative for amyloidosis as such, immunofluorescence and immunohistochemistry technics are helpful to distinguish AA and AL types. Differential diagnostics of AA and AL types guides the treatment strategies. In cases when neither AA nor AL amyloidosis are confirmed, one should consider rare types of amyloidosis, based on the presence of renal involvement—ALECT2, AapolA I, II and IV, AFib or ALys amyloidosis.

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Conflict of interest

Author declares no conflict of interests.

Author details

Elena Zakharova
City Clinical Hospital n.a. S.P. Botkin, Russian Medical Academy of Continuous Postgraduate Education, Moscow, Russian Federation

*Address all correspondence to: helena.zakharova@gmail.com

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