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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.

| | |
|---|---|
| <p>Infectious conditions with persistent inflammation</p> <p><i>Conditions predisposing to chronic infections</i></p> <ul style="list-style-type: none"> • Cystic fibrosis • Epidermolysis bullosa • Paraplegia • Jejunioileal bypass • Intravenous drugs use <p><i>Immunodeficiency's predisposing to chronic infections</i></p> <ul style="list-style-type: none"> • Common variable immunodeficiency • Hypogammaglobulinemia • X-linked agammaglobulinemia • Cyclic neutropenia • HIV/AIDS • Other immunodeficiencies <p><i>Chronic infections</i></p> <ul style="list-style-type: none"> • Bronchiectasis • Osteomyelitis • Tuberculosis • Leprosy • Chronic pyelonephritis • Whipple's disease • Chronic cutaneous ulcers | <p>Chronic non-infectious diseases with persistent inflammation</p> <p><i>Arthritis</i></p> <ul style="list-style-type: none"> • Rheumatoid arthritis • Ankylosing spondylitis • Adult Still disease • Juvenile idiopathic arthritis • Psoriatic arthritis • Gout <p><i>Bowel diseases</i></p> <ul style="list-style-type: none"> • Crohn's disease • Ulcerative colitis <p><i>Systemic vasculitis</i></p> <ul style="list-style-type: none"> • Behcet's disease • Polyarteritis nodosa • Giant cell vasculitis • Takayasu's arteritis • Polymyalgia rheumatica <p><i>Other diseases</i></p> <ul style="list-style-type: none"> • Sarcoidosis • SAPHO syndrome • Schnitzler syndrome • Rosai-Dorfman disease • Recurrent idiopathic pericarditis |
| <p>Neoplastic diseases</p> <p><i>Blood malignancies</i></p> <ul style="list-style-type: none"> • Castleman's disease • Hodgkin's lymphoma • Waldenstrom macroglobulinemia • Hairy cell leukemia <p><i>Solid tumors</i></p> <ul style="list-style-type: none"> • Hepatic adenoma • Renal cell carcinoma • Adenocarcinoma of the lung • Adenocarcinoma of the gut • Mesothelioma | <p>Hereditary autoinflammatory syndromes</p> <p><i>Classic</i></p> <ul style="list-style-type: none"> • Familial Mediterranean fever <p><i>Rare</i></p> <ul style="list-style-type: none"> • TRAPS • Muckle-Wells syndrome • NOMID/CINCA syndrome • Hyper-IgD syndrome • Other monogenic autoinflammatory syndromes |

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.

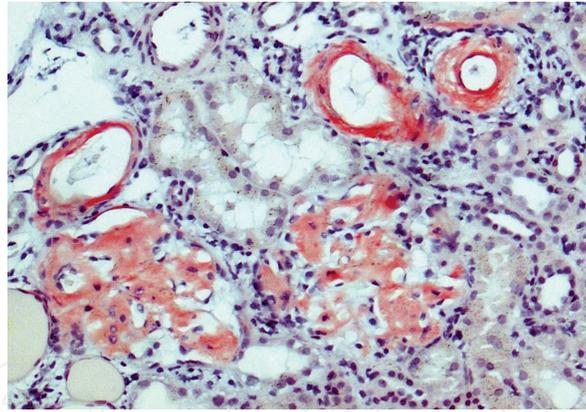


Figure 1.
Renal AA amyloidosis, Congo red 100x.



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.

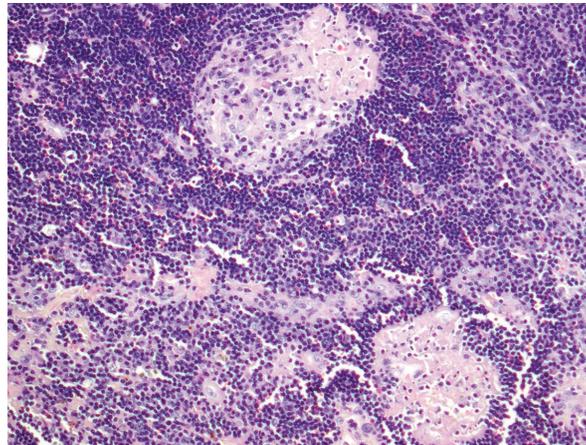


Figure 4.
Castleman's disease, atypical lymphoid tissue, hematoxylin & eosin 100x.



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

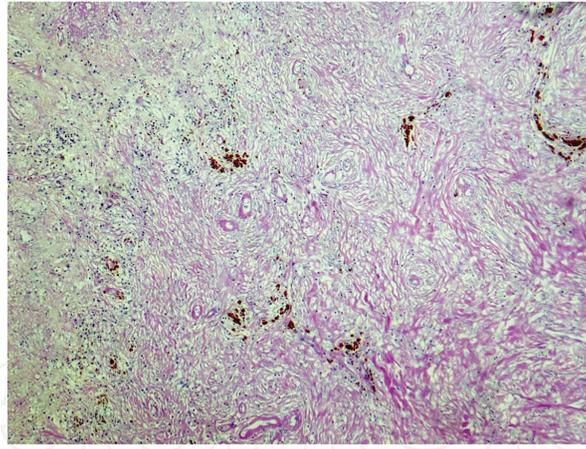


Figure 6.
Sclerosing angiomatoid nodular transformation of the spleen. PAS 100×.

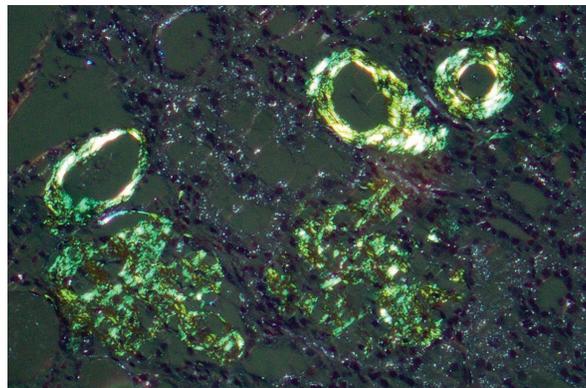


Figure 7.
Renal AA amyloidosis, Congo red 100×, polarized light.

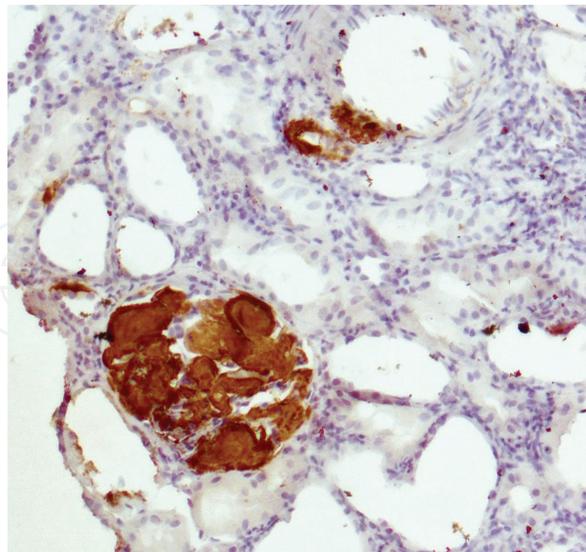


Figure 8.
Renal AA amyloidosis, serum amyloid A, immunoperoxidase 100×.

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**).

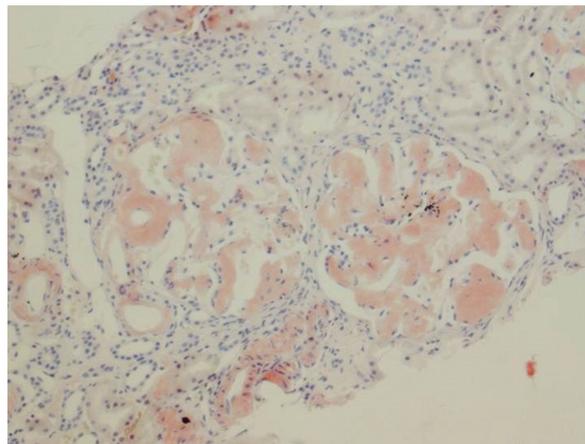


Figure 9.
Renal AL amyloidosis, Congo red 100×.

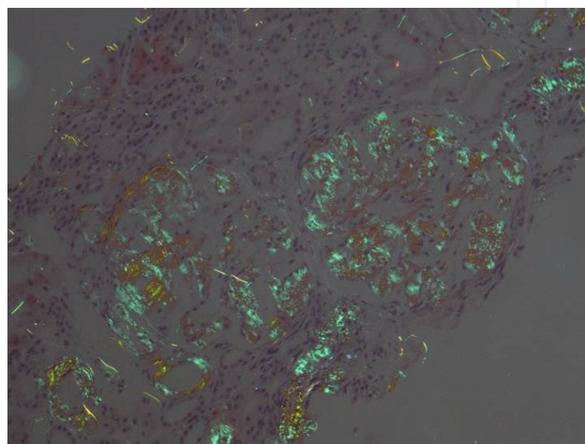


Figure 10.
Renal AL amyloidosis, Congo red 100×, polarized light.

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).

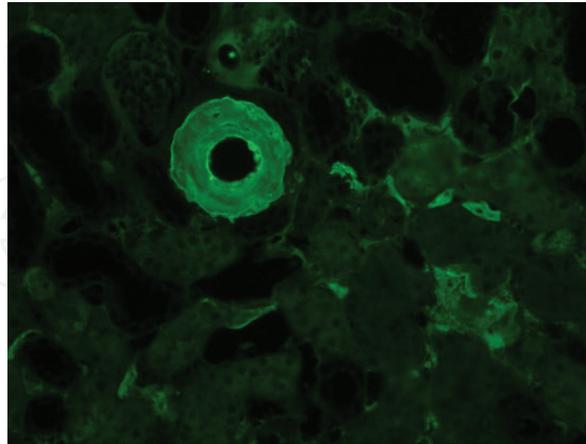


Figure 11.
Renal AL amyloidosis, light chain lambda, immunofluorescence 100x.

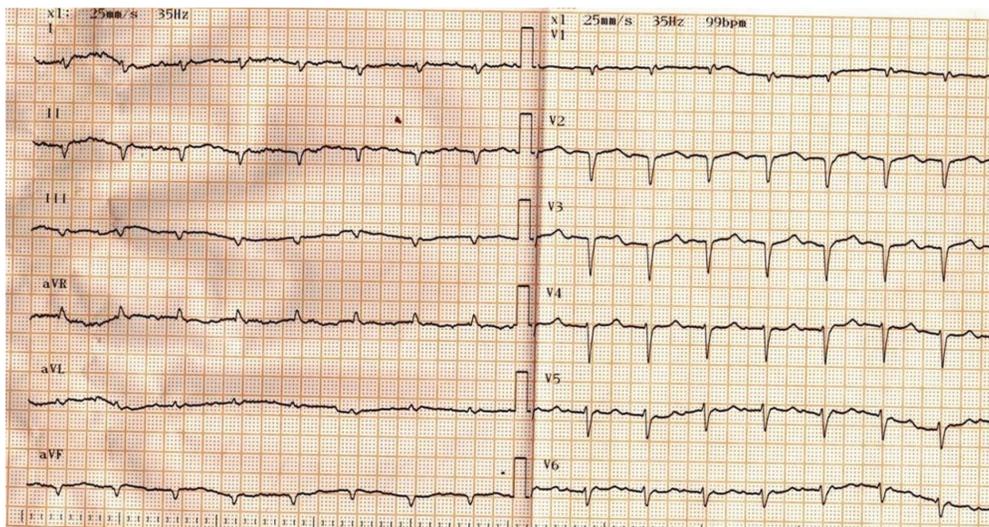


Figure 12.
AL amyloidosis, electrocardiogram, low-voltage waves in all leads.

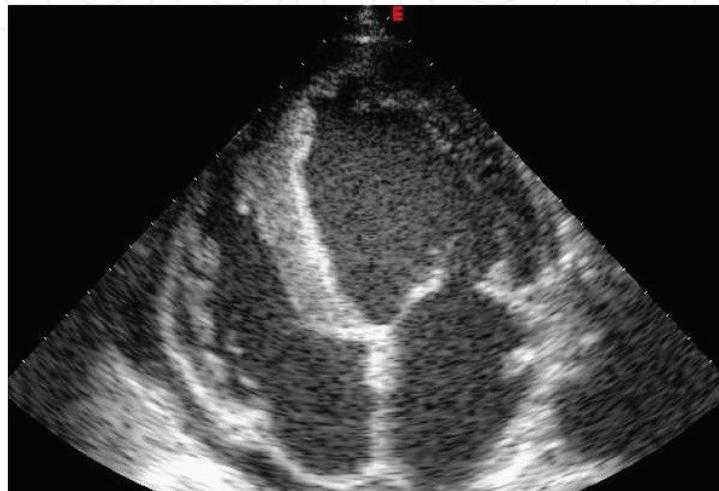


Figure 13.
AL amyloidosis, echocardiogram, myocardial mirror-like appearance.



Figure 14.
AL amyloidosis, macroglossia.



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



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



Figure 17.
AL amyloidosis, spontaneous subcutaneous hemorrhages.

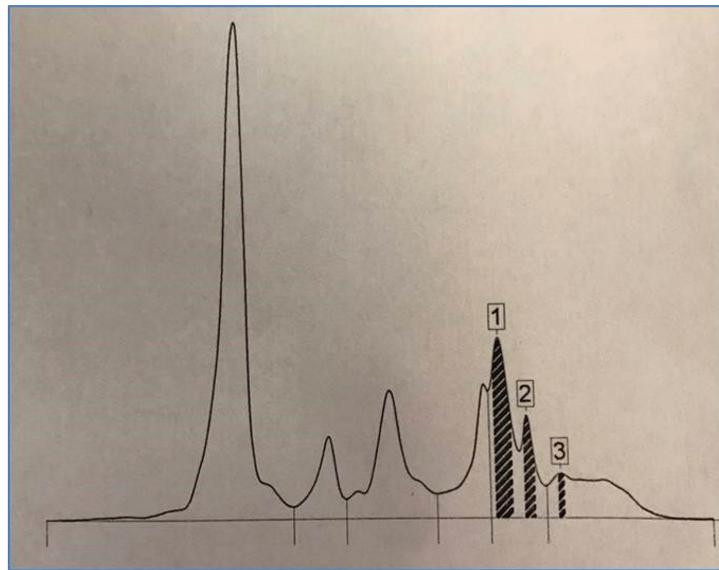


Figure 18.
Serum electrophoresis, M-spike.

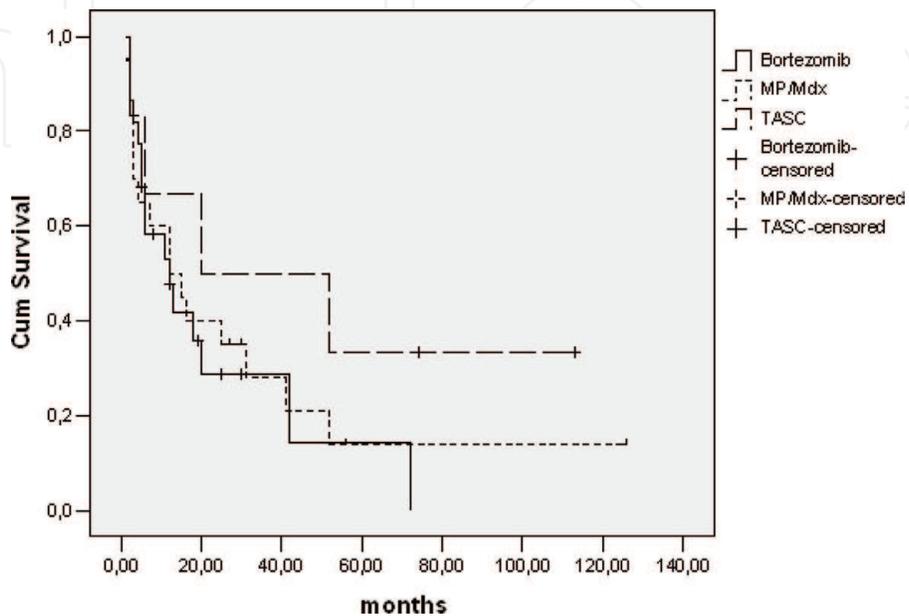


Figure 19.
Treatment results in 49 patients with AL amyloidosis, personal data [23].

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.

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References

- [1] Sipe JD, Benson MD, Buxbaum JN, Ikeda S, Merlini G, Saraiva MJ, et al. Nomenclature 2014: Amyloid fibril proteins and clinical classification of the amyloidosis. *Amyloid*. 2014;**21**(4):221-224. DOI: 10.3109/13506129.2014.964858
- [2] Said SM, Sethi S, Valeri AM, Leung N, Cornell LD, Fidler ME, et al. Renal amyloidosis: Origin and clinicopathologic correlations of 474 recent cases. *Clinical Journal of the American Society of Nephrology*. 2013;**8**:1515-1523
- [3] Picken MM, Dogan A. Amyloidosis of the kidney, the lower urinary and genital tract (male and female) and the breast. In Picken MM, Herrera GA, Dogan A, editors. *Amyloid and Related Disorders*. Totowa, NJ, USA: Humana Press (Springer) 2015. p. 369-390
- [4] Benson MD. The hereditary amyloidoses. In: Picken MM, Herrera GA, Dogan A, editors. *Amyloid and Related Disorders*. Totowa, NJ, USA: Humana Press (Springer); 2015. pp. 65-80
- [5] Lachmann HJ, Goodman HJB, Gilbertson AJ, Gallimore JR, Sabin SA, Gillmore JD, et al. Natural history and outcome in systemic AA amyloidosis. *The New England Journal of Medicine*. 2007;**356**:2361-2371
- [6] Obici L, Merlini G. AA amyloidosis: Basic knowledge, unmet needs and future treatments. *Swiss Medical Weekly*. 2012;**31**:142. DOI: 10.4414/smw.2012.13580
- [7] Ombrello AK, Aksentijevich IAA. Amyloidosis. In: Picken MM, Herrera GA, Dogan A, editors. *Amyloid and Related Disorders*. Totowa, NJ, USA: Humana Press (Springer); 2015. pp. 31-54
- [8] Zakharova EV, Shutov EV, Vorobyova OA, Nikitin EA. AA amyloidosis in a patient with essential thrombocythemia and sclerosing angiomatoid nodular transformation of the spleen. *Journal of Onco-Nephrology*. 2017;**1**(3):13-17. DOI: 10.5301/jo-n.5000028
- [9] Kyle RA, Linos A, Beard SM, Linke RP, Gertz MA, O'Fallon WM, et al. Incidence and natural history of primary systemic amyloidosis in Olmsted County, Minnesota, 1950 through 1989. *Blood*. 1992;**79**:1817-1822
- [10] Pinney JH, Smyth CJ, Taube JB, Lachmann HJ, Venner CP, Gibbs SD. Systemic amyloidosis in England: An epidemiological study. *British Journal of Haematology*. 2013;**161**:523-532
- [11] Herrera G, Picken M. Renal diseases associated with plasma cell dyscrasias, amyloidosis, Waldenstrom macroglobulinemia and cryoglobulinemic nephropathies. In: Jennette J, Olson J, Silva F, D'Agati V, editors. *Heptinstall's Pathology of the Kidney*. 7th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2014. pp. 951-114
- [12] Blade J, Fernandez-Llama P, Bosch F, Montoliu J, Lens XM, Montoto S. Renal failure in multiple myeloma: Presenting features and predictors of outcome in 94 patients from a single institution. *Archives of Internal Medicine*. 1998;**158**(17):1889-1893
- [13] Cohen AH, Zhou P, Xiao Q, Fleisher M, Kalakonda N, Akhurst T, et al. Systemic AL amyloidosis due to non-Hodgkin's lymphoma: An unusual clinicopathologic association. *British Journal of Haematology*. 2004;**124**:309-314
- [14] Ikee R, Kobayashi S, Hemmi N, Suzuki S, Miura S. Amyloidosis associated with chronic lymphocytic leukemia. *Amyloid*. 2005;**12**:131-134
- [15] Gertz M, Kyle R. The plasma cell labelling index: A valuable tool in

primary systemic amyloidosis. *Blood*. 1989;**74**:1008-1011

[16] Gertz M, Kyle R, Noel P. Primary systemic amyloidosis: A rare complication of immunoglobulin M monoclonal gammopathies and Waldenstrom's macroglobulinemia. *Journal of Clinical Oncology*. 1993;**11**:914-920

[17] Merlini G, Stone MJ. Dangerous small B-cell clones. *Blood*. 2006;**108**(8):2520-2530

[18] Said S, Sethi S, Valeri A, Leung N, Cornell L, Fidler ME, et al. Renal amyloidosis: Origin and clinicopathologic correlations of 474 recent cases. *Clinical Journal of the American Society of Nephrology*. 2013;**8**:1515-1523

[19] Gertz M, Lacy M, Dispenzieri A. Immunoglobulin light chain amyloidosis and the kidney. *Kidney International*. 2002;**61**:1-9

[20] Gertz M, Leung N, Lacy MQ, Dispenzieri A, Zeldenrust SR, Haymann SR, et al. Clinical outcomes in immunoglobulin light chain amyloidosis affecting kidney. *Nephrology Dialysis Transplantation*. 2009;**24**:3132-3137

[21] Falk R, Comenzo R, Skinner M. The systemic amyloidosis. *The New England Journal of Medicine*. 1997;**337**:898-909

[22] Fermand J-P, Bridoux F, Kyle RA, Kastiris E, Weiss BM, Cook MA, et al. On behalf of the international kidney and monoclonal Gammopathy research group. How I treat monoclonal gammopathy of renal significance (MGRS). *Blood*. 2013;**122**(22):3583-3590

[23] Zakharova EV, Stolyarevich ES. Chemotherapy for renal AL amyloidosis: Treatment results and outcomes in 49 patients from a single center. *Clinical Practice*. 2016;**13**(1):11-18