Case Report

Solitary Renal Impairment in a 68-Year-Old Patient Caused by an α-Fibrinogen Amyloidosis

Monika Beliančinová¹,², Patrícia Kleinová¹,²*, Matej Vnučák¹,², Karol Graňák¹,², Jana Kršiaková³, Patrik Flódr⁴, Marián Mokáň², Ivana Dedinská¹,²

¹Transplant Centre, University Hospital Martin, Kollárova 2, 036 01 Martin, Slovakia
²Department of Internal Medicine, University Hospital Martin, Jessenius Medical Faculty, Comenius University, 036 01 Martin, Slovakia
³Department of Genetics, University Hospital Martin, Kollárova 2, 036 01 Martin, Slovakia
⁴Department of Clinical and Molecular Pathology, Faculty of Medicine, Palacký University Olomouc, 779 00 Olomouc, Czech Republic

*Corresponding Author: Patrícia Kleinová, Transplant Centre, University Hospital Martin, Department of Internal Medicine, Jessenius Medical Faculty, Comenius University, Kollárova 2, 036 01 Martin, Slovakia.


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Abstract

Amyloidosis represents a spectrum of serious diseases characterized by the deposition of excessive deposits of incorrectly confirmed proteins (amyloid structures) in extracellular spaces. Deposits tend to be only in one organ or the entire organ system. This disease can lead from minor organ damage to life-threatening conditions and death within a relatively short period. Currently, the most widely used diagnostic method for the diagnosis of amyloidosis is mass spectrophotometry and proteomic analysis, with the help of which it is possible to identify the type of amyloid and determine an adequate therapeutic procedure. We present a patient with fully developed nephrotic syndrome and a decline in kidney function. In addition, α-fibrinogen amyloidosis was confirmed based on proteomic analysis of a kidney biopsy sample.

Keywords: Amyloidosis; Alpha Fibrinogen; Kidneys

Introduction

Amyloidosis is a common name for several serious diseases, the common characteristic of which is the deposition of incorrectly confirmed otherwise soluble proteins (amyloid) in extracellular spaces. The type of amyloidosis varies according to the type of amyloid and where it is deposited. When the diagnosis is clarified, the affected organ is usually severely damaged. In the case of affecting several organs, the damage can be so severe that it leads to life-threatening conditions and death within a short period. Unfortunately, this disease has a low incidence. Therefore, it is often overlooked because of incorrectly chosen diagnostic procedures, leading to false negative results and delays in adequate treatment.

The character and progression of the disease depend on the kinetics of amyloid formation and the method of its degradation. The diagnosis is based on unequivocal evidence in the form of tissue histology of the affected organ. However, evidence of the presence of amyloid by staining with Congo red is limited, which leads to an apple-green dichroic effect in polarized light microscopy. Other diagnostic methods, such as mass spectrophotometry and proteomic analysis, help identify a specific type of amyloid. We can identify several types of hereditary and acquired amyloidosis using proteomic analysis. The most common hereditary amyloidosis include, for example, AL amyloidosis (light chain amyloidosis), AA amyloidosis (A amyloidosis), TTR (transthyretin) amyloidosis or β2-microglobulin amyloidosis, which it can also be classified as acquired amyloidosis, but a hereditary form has also been proven. An α-fibrinogen amyloidosis is a rare type with approximately 30 other subtypes. Individual subtypes of amyloidosis and specific mutations can only be identified by genetic analysis (Table 1).

<table>
<thead>
<tr>
<th>Type of Amyloidosis</th>
<th>Protein Type</th>
<th>Type of Amyloidosis</th>
<th>Organ Involvement</th>
</tr>
</thead>
<tbody>
<tr>
<td>AL amyloidosis</td>
<td>Immunoglobulin light chain</td>
<td>Acquired</td>
<td>Kidney, heart, liver, gastrointestinal tract, spleen, nervous system, soft tissue, thyroid, adrenal gland</td>
</tr>
<tr>
<td>AH amyloidosis</td>
<td>Immunoglobulin heavy chain</td>
<td>Acquired, myeloma</td>
<td>Rare; kidney involvement, a small number of reported cases</td>
</tr>
<tr>
<td>Senile systemic amyloidosis</td>
<td>Transthyretin (wild type)</td>
<td>Accumulation of TTR</td>
<td>Heart, soft tissue</td>
</tr>
<tr>
<td>Familiar amyloid polyneuropathy</td>
<td>Transthyretin, gelsolin, Apo AI</td>
<td>Inherited</td>
<td>Neuropathy, heart, eye, soft tissue</td>
</tr>
<tr>
<td>AA amyloidosis (secondary)</td>
<td>SAA protein</td>
<td>Acquired, chronic disease</td>
<td>Kidney, liver, gastrointestinal tract, spleen, autonomic nervous system, thyroid</td>
</tr>
<tr>
<td>Aβ2M amyloidosis</td>
<td>β2-microglobulin</td>
<td>Chronic dialysis</td>
<td>Osteoarticular tissue; less common sites are the gastrointestinal tract, blood vessels, heart</td>
</tr>
<tr>
<td>Lyzosyme amyloidosis (ALyz)</td>
<td>Lysozyme</td>
<td>Inherited</td>
<td>Kidney, liver, gastrointestinal tract, spleen, lymph nodes, lungs, thyroid, salivary glands</td>
</tr>
<tr>
<td>Apo AI amyloidóza (AApol)</td>
<td>Apolipoprotein AI</td>
<td>Inherited</td>
<td>Kidney (with predominant medullary deposition), liver, heart, skin, larynx</td>
</tr>
<tr>
<td>Apo AII amyloidosis (AApoII)</td>
<td>Apolipoprotein AII</td>
<td>Inherited</td>
<td>Kidney</td>
</tr>
</tbody>
</table>
### Table 1: Types of some of the hereditary and acquired amyloidoses (21-28)

<table>
<thead>
<tr>
<th>Type of Amyloidosis</th>
<th>Associated Protein</th>
<th>Inheritance</th>
<th>Location</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apo AIV amyloidosis (AApoIV)</td>
<td>apolipoprotein AIV</td>
<td>Inherited</td>
<td>Kidney</td>
</tr>
<tr>
<td>Fibrinogen amyloidosis (AFib)</td>
<td>Aα chain fibrinogen</td>
<td>Inherited</td>
<td>Kidney, liver, and spleen; hypertension is familiar; kidney involvement is predominantly glomerular</td>
</tr>
<tr>
<td>Gelsolin amyloidosis (AGel)</td>
<td>gelsolin</td>
<td>Inherited</td>
<td>Cranial nerves, lattice corneal dystrophy</td>
</tr>
<tr>
<td>Amyloid angiopathy, Icelandic type (ACys)</td>
<td>Cystatin C</td>
<td>Inherited</td>
<td>Cerebral vessels</td>
</tr>
<tr>
<td>Familiar British dementia (BriPP a.)</td>
<td>Product of BRI2 gene</td>
<td>Inherited, stop codon</td>
<td>Vessels, brain parenchyma</td>
</tr>
<tr>
<td>Acquired renal amyloidosis (ALECT2)</td>
<td>Leucocytes chemotactic factor 2</td>
<td>acquired</td>
<td>Kidney</td>
</tr>
<tr>
<td>Aortic median amyloidosis (AMed)</td>
<td>cadherin</td>
<td>Form of AA amyloidosis</td>
<td>Arteries</td>
</tr>
<tr>
<td>Atrial amyloidosis (AANF)</td>
<td>Atrial natriuretic factor</td>
<td>Patients with atrial fibrillation</td>
<td>Heart</td>
</tr>
<tr>
<td>Amyloidosis associated with medullary carcinoma</td>
<td>calcitonin</td>
<td>Malignant disorders</td>
<td>Thyroid gland</td>
</tr>
<tr>
<td>Spongiform encephalopathy (AScr)</td>
<td>prion</td>
<td>Acquired</td>
<td>Brain</td>
</tr>
<tr>
<td>Islet polypeptide amyloidosis</td>
<td>Islet amyloid polypeptide</td>
<td>Langerhans isles, DM 2, insulinoma</td>
<td>Pancreatic tissue</td>
</tr>
<tr>
<td>Lactoferrin amyloidosis (ALac)</td>
<td>lactoferrin</td>
<td>Familiarity corneal amyloidosis</td>
<td>Corneal deposits, pancreas</td>
</tr>
<tr>
<td>Alzheimer’s disease</td>
<td>amyloid β precursor protein</td>
<td>Acquired</td>
<td>Brain tissue</td>
</tr>
<tr>
<td>Hereditary cerebral amyloidosis (Aβ)</td>
<td>amyloid β precursor protein</td>
<td>Inherited</td>
<td>Small vessels of the brain</td>
</tr>
</tbody>
</table>
The first sign of amyloidosis is often kidney function impairment due to amyloid deposition in glomerules, but some signs and symptoms occur before organ damage. These symptoms are often non-specific, like problems with breathing, malaise, fatigue, nausea, poor appetite, weight loss, headache, vertigo, diarrhea, acral dysesthesia, problems with speaking, enlarged tongue with rippled edges, swelling of lower limbs, palpitations, syncope, etc. [1].

In Slovakia, there hasn’t been documented case of alpha fibrinogen amyloidosis yet, possibly according to a small number of inhabitants (approximately 5,447 million). Still, there are several reported cases of AA amyloidosis or AL amyloidosis. In the United Kingdom, data suggest the incidence of systemic amyloidosis to 0,8/100,000 of the inhabitants [2]. Alpha Fibrinogen Amyloidosis (Afib) is a sporadic condition in general but the most prevalent type of hereditary amyloidosis in the United Kingdom (approximately 71 cases) [3]. In Asia, there are only five documented cases (Korea, China, Japan) [4].

Case Report

A 68-year-old man without a severe illness was hospitalized at the Department of Internal Medicine of Martin University Hospital for a fully developed nephrotic syndrome with retention of nitrogenous substances in 2019. After a complex diagnostic process, he was diagnosed with chronic kidney disease based on hypertensive nephropathy and possibly uric acid nephropathy. However, because of the progression of proteinuria and retention of the nitrogenous substances, the patient was referred to the Transplantation Centre of Martin University Hospital. Medical history includes arterial hypertension and the presence of methyl-tetrahydrofolate reductase polymorphism with fibrinogen gene mutation.

The patient complained about lower limb swelling and weight gain progression when admitted to our center. He also noticed increased tiredness, and the urine was often foamy. Although the patient also complained of arterial hypertension in the 150-160/85-90 mmHg range, he denied any other problems. At the time of admission to our center, we performed routine laboratory examinations, with the finding of retention of nitrogenous substances and proteinuria of 3.8 grams/24 hours. The objective result was only the swelling of the lower limbs up to the knees. During the hospitalization in the center, we started complex therapy for the nephrotic syndrome using loop diuretics and intravenous infusions of human albumin. After regressing the swelling and restoring the values of serum albuminemia, we performed a kidney biopsy. We did not detect any circulating autoantibodies.

After staining the histological sample of the kidney with Congo red, we proved the presence of amyloid in the form of massive glomerular deposits. (Figures 1-3)
Figure 3: Detail of the completely destructed glomerule with the amyloid deposition after staining with Congo red (Congo red, original magnification: 125x).

The patient subsequently underwent a complex diagnostic process to determine the range of the disease, including roentgen and sonographic examination of the body, which remained negative. We added High Resolution Computed Tomography (HRCT) examination of the lungs, which showed no signs of lung parenchyma or mediastinal lymphadenopathy involvement. Eye examination revealed angiopathic retinal changes in poorly controlled arterial hypertension with mild optic nerve papilla atrophy without amyloid. We have also added endoscopic examinations of the digestive tract. On the gastrofibroscopic review, only erosion of the gastric antrum was present; the colonoscopy showed colonic diverticulosis without acute diverticulitis. During both examinations, we took samples to examine the presence of amyloid with a negative result. Due to cold acrodyesthesiae, on the recommendation of a neurologist and an ophthalmologist, we completed the examination process with Magnetic Resonance Imaging (MRI) of the brain and orbit with the finding of non-specific areas of gliosis in the brain without signs of orbital amyloidosis. Routine laboratory tests showed increased serum levels of kappa and lambda light chains with a physiological ratio and an isolated increase in Immunoglobulin E (IgE) and β2-microglobulin. Still, we did not detect the presence of Bence-Jones protein in the urine. Furthermore, the results of immunofixation in serum and urine were negative. Therefore, we consulted a hematologist and proceeded to a trepanobiopsy of the bone marrow, excluding monoclonal myeloma cells. Also, we excluded the presence of amyloid deposits in various organ systems endoscopically and histologically. Then, we proceeded to DNA analysis of the serum, which did not confirm the pathogenic variant that would be causal for transthyretin amyloidosis. Therefore, we performed a proteomic analysis of a histological kidney sample.

Finally, in cooperation with pathologists, we proved the presence of alpha-fibrinogen amyloidosis with dichroism and apple-green birefringence in polarized light microscopy.

Using an immunohistochemical examination, we detected the positivity of fibrinogen of medium intensity (background), Immunoglobulin G (IgG) of low to medium intensity, without convincing positivity (only with very little intense positivity) AA, kappa, lambda, TTR, lysozyme, IgA, IgM, IgD (Figure 4).

Figure 4: Immunohistochemical proof of fibrinogen presence in glomerule (anti-fibrinogen antibody, original magnification: 125x).

The material was limited in volume, but with the use of proteomic analysis and service of the sample Laser Microdissection Method and Liquid Chromatography-Tandem Mass Spectrometry (LMD-LC/MS), we found the most abundant amyloid fibrillary protein fibrinogen alpha chain, which was relatively represented in the sample by 1.12%, P-score 23.0 %, D-score 23.0%. The relative abundance of serum amyloid P component (APCS), apolipoprotein E (APOE), and apolipoprotein A4 (APOA4) was 4.962%, 3.353%, and 1.955%, respectively. Considering the type of amyloidosis, its heredity, and the number of possible subtypes, we decided to perform a genetic analysis, which verified variant c.1634A>T, p.(Glu545Val) heterozygote, which is a missense variant of FGA gene in the exome No5. After this finding, we decided to test all of the first-line descendants of the patient and relatives, and we confirmed the alpha fibrinogen amyloidosis variant in the patient’s sister, daughter, and son. Also, in this patient, the kidney impairment has been in rapid progression since the diagnosis, and the patient is in preparation for renal replacement therapy (RRT). At first, he will enter a dialysis program and be included on the waiting list for kidney transplantation (KTx). The patient agreed with the processing and publication of the case report and signed the informed consent.
Discussion

Amyloidosis is a rare disease that is often overlooked or underdiagnosed. The kidneys are usually the first organ affected. Still, patients with progression of nitrogen substances retention and poorly controlled arterial hypertension are often diagnosed with hypertensive nephropathy, interrupting the diagnostic process. Amyloidosis is a disease that usually affects entire organ systems and can lead to fatal consequences in a relatively short period. Several types of amyloidosis are hereditary. Therefore, examining the affected patient’s first-line descendants is advisable to prevent the disease’s consequences in early detection or considering potential organ donation.

Confirmation of the diagnosis of amyloidosis depends on examining a histological sample of the affected organ tissue. When using conventional hematoxylin and eosin staining, specimens have a hyaline appearance [5]. In light microscopy, it can be reliably detected only using Congo red dye, which is not commonly used and requires examination by an experienced histopathologist [6]. AFib is characterized by a unique picture of severe glomerular involvement with almost complete replacement of the glomeruli with amyloid deposits without the participation of the surrounding vessels and interstitium [5,7]. Once the diagnosis is confirmed, it is appropriate to determine the exact type of amyloid, which is essential to decide on further proper management and treatment.

Immunohistochemical and proteomic analysis are the most widely used techniques, performed only in some laboratories and in the case of immunohistochemical examination. Still, there are limits in the analysis due to the need for available laboratory-prepared reagents - autoantibodies, which would be suitable for cross-reaction with amyloid and for their questionable sensitivity. Therefore, proteomic analysis remains the most specific and sensitive examination used for diagnosing and typing AFib. This type of amyloidosis is the most common form of hereditary amyloidosis. It affects only the kidneys, or it affects the heart or causes neurological deficits. Therefore it is considered systemic amyloidosis [8,9]. Fibrinogen is a soluble glycoprotein composed of trimers with a mass of 340 kDa. It is an irreplaceable part of the coagulation cascade. It is also used as a reactant in the acute phase of inflammation as a bridge of molecular communication between cells. Its quantity increases during traumatic events, in a septic state, and during pregnancy, when it is increased two to tenfold. Each trimer is composed of one Aα, one Bβ, and one γ chain encoded by the closely linked genes FGA, FGB, and FBG, located on chromosome 4, on arms q23 and q32, respectively [10]. 1.5-7 grams of this glycoprotein are produced daily in the liver [11]. A mutation in one or both FGA genes causes autosomal dominant Aα-fibrinogen amyloidosis. The abnormally conformed protein occurs in the bloodstream and, with its excessive production and reduced degradation, is deposited in the affected organs. This subsequently leads to decreased function and gradual failure [12]. Persons with such a mutation are predisposed to blood coagulation disorders in the sense of higher susceptibility to the formation of clots or increased bleeding. Currently, there are no known cases where a mutation in a gene other than the FGA gene has been proven in the case of confirmed AFib [13]. Patients with AFib are most often referred for renal biopsy because of proteinuria, hypotension, and a rapid decline in renal function to end-stage renal failure with the need for renal replacement therapy within 1-5 years of the diagnosis [5].

Treatment of amyloidosis depends on the type of amyloid structure. Current treatment management for AL amyloidosis is to lower or eradicate the clonal plasma cells which produce the amyloidogenic light chain fibrils. AL amyloidosis’s prognosis has improved over the past decade with aggressive anti-plasma cell treatment.

The current approach to treating AA amyloidosis is to treat the underlying chronic inflammatory or malignant disease, thereby reducing the production and deposition of serum amyloid A. The first line of treatment is the use of colchicine, which is often life-long and inhibits associated inflammation and prevents the development of organ failure in many patients. However, after genetic analysis, many other therapeutic approaches exist, including monoclonal antibodies, anti-TNF-α, and anti-IL-6 agents [14].

The curative therapy method of AFib is kidney transplantation, but due to the constant production of misfolded protein, further damage occurs to both the transplanted kidney and other affected organs [15,16]. In the case of a kidney transplant, the probability of graft failure within seven years after transplantation is almost inevitable. The 10-year horizon of graft survival is only 5.5% of patients [5,17-20]. Combined liver and kidney transplantation is currently the only effective curative method that can stop the further progression of the disease. However, separate liver transplantation or combined transplantation of both organs should be considered before the failure of native kidneys and significant damage to other organ systems [21].

Conclusions

This case study presents an unusual form of hereditary amyloidosis with progressive loss of renal functions. Amyloidoses constitute a group of diseases in which proteins deposit extracellularly in tissues as insoluble fibrils. Many treatment methods are known, but the only curative process for α fibrinogen amyloidosis seems to be liver and kidney transplantation. This case report highlights the importance of comprehensive diagnostic procedures and teamwork in identifying this rare but often fatal...
diagnosis if it remains undiagnosed.

Disclosure


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Institutional Review Board Statement: All experimental procedures were approved by the Ethics Committee of the Jessenius Faculty of Medicine Comenius University and conformed to the principles outlined in the Declaration of Helsinki. This study was guided by ethical standards and national and international laws. The patient signed the consent form after receiving instructions regarding the possible risks and benefits and was granted privacy, confidentiality, and anonymity rights. The patient was free to stop participating at any stage of the experiment without giving reasons for their decision.

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study. Written informed consent has been obtained from the patient(s) to publish this paper.

Data Availability Statement: Data supporting the study results can be provided followed by request sent to the corresponding author’s e-mail.

Conflicts of Interest: None.

References

4. Picken MM, Dogan A. Amyloidoses of the Kidney, the Lower Urinary and Genital Tracts (Male and Female), and the Breast In Picken MM, Herrera GA, Dogan A, editors. Amyloid and Related Disorders. 2nd ed: Humana; 2015. p. 369–389


