Canadian Society of Nephrology/ Société canadienne de néphrologie CSN/SCN

CANADIAN JOURNAL OF KIDNEY HEALTH AND DISEASE
Journal canadien de la santé et de la maladie rénale

Research Case Report

Canadian Journal of Kidney Health and Disease
Volume 10: 1–6

DOI: 10.1177/20543581231209207
journals.sagepub.com/home/cjk

Sage

De Novo Fibrinogen A Alpha Chain Amyloidosis in a Kidney Transplant Patient: Case Report and Literature Review

Taqui Khaja[1], Luan Truong[2], and George Nassar[1,3,4]

Abstract

Rationale: *De Novo* transplant amyloidosis denotes the condition when a patient develops amyloidosis after transplantation but had not been diagnosed with the disease prior to transplantation. The incidence of *de novo* amyloidosis in kidney transplants is rare, but few published case reports have described the occurrence of *de novo* Amyloid A protein (AA) and Light Chain (AL) amyloidosis. However, *de novo* hereditary fibrinogen A alpha chain (AFib) has not been previously reported.
Patient Presentation: We present a 72-year-old man, a kidney transplant recipient, who developed progressive rise in his creatinine about 3 years after transplantation. He has long-standing diabetes mellitus type 2, obesity, and hypertension, so he did not have a kidney biopsy of his native kidneys prior to transplantation.
Diagnosis: A kidney transplant biopsy was done that showed amyloidosis. Mass spectrophotometry confirmed it as AFib amyloidosis. Genetic testing of the patient revealed that he has fibrinogen A alpha gene (FGA) point mutation with a p.E545V variant.
Interventions: Cardiac evaluation showed normal transthoracic echocardiogram. Cardiac magnetic resonance imaging (MRI) showed no involvement by amyloidosis. A peripheral nerve biopsy showed diabetic neuropathy. Thus, the kidney was the only organ involved by the disease. The kidney transplant was managed conservatively with blood pressure and diabetes control in addition to his usual immunosuppression regimen which was not altered. He is being treated with diuretics, angiotensin receptor inhibitors, and sodium glucose transport 2 inhibitors.
Outcomes: Kidney transplant function exhibited only slow progression over 18 months since the diagnosis was confirmed. This slow progression is likely because the p.E545V point mutation variant is less aggressive than other gene deletion mutations and because our patient was judged to have been diagnosed early in the course of his disease.
Teaching Points: In this case report, we illustrate the findings and testing that confirmed the diagnosis of AFib amyloidosis. We summarize the clinical aspects, outcomes of the disease, and treatment options. We believe this case report is interesting because it is the first reported case of AFib amyloidosis in a kidney transplant recipient who was not known to have the disease prior to kidney transplantation.

Abrege

Justification: L'amyloïdose *de novo* de la transplantation désigne l'état d'un patient qui développe une amylose après une transplantation alors que la maladie n'avait pas été diagnostiquée avant l'intervention. L'incidence de l'amyloïdose *de novo* est rare en contexte de transplantation rénale, bien que la survenue d'amyloses AA et AL *de novo* ait été décrite dans quelques rapports de cas publiés. L'amyloïdose *de novo* héréditaire de la chaîne alpha du fibrinogène A (FibA) n'a cependant jamais été rapportée.
Présentation du patient: Nous présentons le cas d'un homme de 72 ans, receveur d'une greffe rénale, dont le taux de créatinine a augmenté progressivement environ trois ans après la transplantation. Le patient souffrait depuis longtemps de diabète de type 2, d'obésité et d'hypertension, de sorte qu'il n'avait pas subi de biopsie de ses reins d'origine avant la transplantation.
Diagnostic: Une biopsie du greffon rénal a montré une amyloïdose, laquelle a ultérieurement été typée par spectrophotométrie de masse comme étant une amyloïdose FibA. Des tests génétiques ont révélé que le patient présentait une mutation ponctuelle du gène alpha du fibrinogène (FGA) avec le variant p.E545V.
Interventions: L'échocardiogramme transthoracique du bilan cardiaque était normal. L'IRM cardiaque n'a montré aucune implication par amyloïdose, et une biopsie des nerfs périphériques a révélé une neuropathie diabétique. Ainsi, le rein était le

seul organe touché par la maladie. La greffe rénale a été gérée de manière conservatrice, soit par le contrôle de la pression artérielle et du diabète en plus du schéma habituel d'immunosuppression, lequel n'a pas été modifié. Le patient est traité avec des diurétiques, des inhibiteurs des récepteurs de l'angiotensine et des inhibiteurs du cotransport sodium-glucose de type 2.
Résultats: La fonction du greffon n'a montré qu'une lente progression sur 18 mois depuis la confirmation du diagnostic. Cette lente progression est probablement due au fait que la mutation ponctuelle p.E545V est moins agressive que d'autres mutations de délétion du gène, et parce que notre patient a été jugé comme ayant reçu son diagnostic tôt dans l'évolution de sa maladie.
Enseignements tirés: Dans ce rapport de cas, nous mettons en évidence les résultats et tests qui ont confirmé le diagnostic d'amyloïdose FibA. Nous résumons les aspects cliniques, le pronostic de la maladie et les options de traitement. Ce rapport de cas est intéressant, car il s'agit du premier cas rapporté d'amyloïdose FibA chez un receveur d'une greffe rénale sans diagnostic connu de la maladie avant la transplantation.

Keywords
kidney transplantation, hereditary, amyloidosis, fibrinogen A alpha chain, mutation

Received April 29, 2023. Accepted for publication September 21, 2023.

Introduction

A white male developed end-stage kidney disease (ESKD) at the age of 61 years and was placed on hemodialysis in 2011. He did not have a native kidney biopsy because his ESKD was attributed to be due to long-standing poorly controlled type 2 diabetes mellitus (>20 years), obesity (body mass index 35), and hypertension (>15 years). He subsequently received a deceased donor kidney transplant in April 2018. He was considered a low immunological risk (0% plasma reactive antibodies to Class I and II), had basiliximab (Simulect, Novartis, Basel, Switzerland) induction, and was maintained on tacrolimus, mycophenolate, and prednisone.

Presenting Concerns

At about 3 years after transplantation (January-April 2021), his serum creatinine rose from a previously established baseline of 88.4 to 97.3 μmol/l to reach levels of 115.0 to 123.8 μmol/l. This raised concerns about an ongoing disease of his kidney transplant.

Clinical Findings

At the time of kidney transplantation, the patient was already requiring insulin injections and frequently had an HbA1c > 8.0%. He suffered from morbidities that were attributable to diabetes such as peripheral neuropathy for which he was on gabapentin, peripheral vascular disease, and 3+ dipstick proteinuria. He had a history of coronary artery disease that required coronary stent placement in 2016 and had sleep apnea for which he was on continuous positive airway pressure (CPAP) support. His physical examination was most relevant for obesity and pedal edema. The initial workup in response to the rise of his creatinine in April 2021 revealed a bland urinalysis, urine protein to creatinine ratio of 0.1 (normal < 0.15), and absence of donor-specific antibodies. His blood polyomavirus and cytomegalovirus tests were undetectable by PCR. His tacrolimus blood levels were in the target range around 6 ng/ml. His kidney transplant ultrasound revealed no abnormality. By August 2021, his creatinine further rose to reach 159.2 μmol/l, so a kidney transplant biopsy was performed.

Diagnostic Focus and Assessment

The kidney transplant biopsy was interpreted as follows: On light microscopy, it showed an element of mesangial expansion, but there were no signs of inflammation or transplant rejection (Figure 1A-D). The total estimate of interstitial fibrosis and tubular atrophy (IFTA) was less than 10%. The striking finding however was the positive Congo Red staining for amyloid deposits in the mesangium (Figure 1E). Texas Red Filter fluorescence microscopy confirmed the presence of congophilic amyloid deposits (Figure 1F). The amyloid deposits stained positive for IgM and C4d but stained negative for kappa and lambda chains (Figure 2). The electron microscopy revealed amyloid fibrils (Figure 3). In order to further classify the amyloid type, the biopsy specimen was subjected to mass spectrometry. This showed that the amyloid deposits were due to fibrinogen A alpha chain (AFib) amyloidosis. Genetic testing of the patient using the Natera Renasight Kidney Gene Panel revealed the presence

[1]Division of Nephrology, Department of Internal Medicine, Houston Methodist Hospital, Weill Cornell Medicine, TX, USA
[2]Department of Pathology, Houston Methodist Hospital, Weill Cornell Medicine, TX, USA
[3]Nephrology, Dialysis & Transplantation Associates, Houston, TX, USA
[4]Panoramic Health, Tempe, AZ, USA

Corresponding Author:
George Nassar, Nephrology, Dialysis & Transplantation Associates, 6560 Fannin Street, Scurlock Tower, Suite 1824, Houston, TX 77030, USA.
Email: gmnassar@houstonmethodist.org

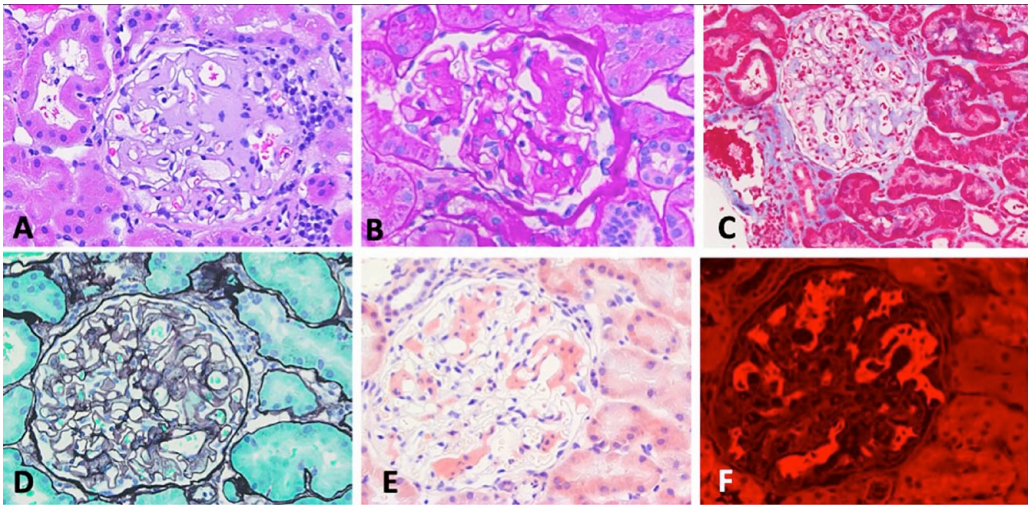

Figure 1. Light microscopy and Texas Red filtered immunofluorescent microscopy show glomerular amyloid deposition causing mesangial expansion: (A) hematoxylin & eosin stain; (B) periodic acid-Schiff stain; (C) trichrome stain; (D) silver methenamine stain; (E) Congo Red stain; (F) Congo Red stain under Texas Red-filtered immunofluorescent microscopy (all panels ×400).
Note. Glomerular amyloid deposition causing mesangial expansion.

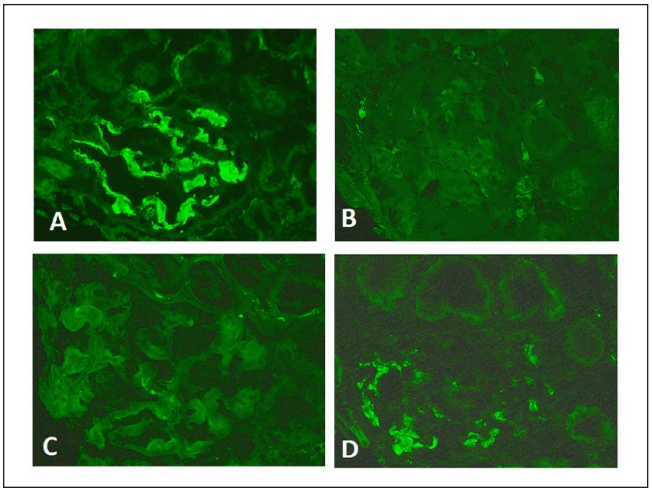

Figure 2. Immunofluorescent microscopy findings: (A) The amyloid deposition is strongly decorated by C4d, but there is no significant staining of peritubular capillaries for C4d; (B) the amyloid is negative for kappa light chain; (C) the amyloid is negative for lambda light chain; (D) the amyloid is positive for IgM (all panels ×400).

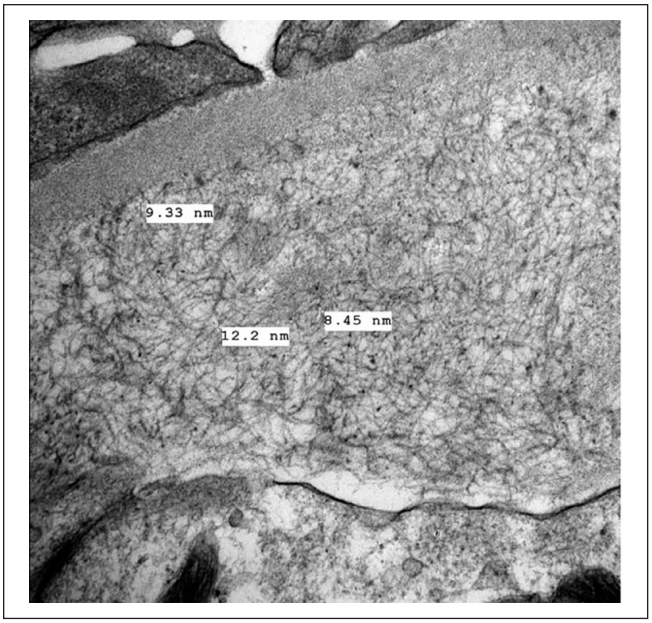

Figure 3. Amyloid fibrils demonstrated by electron microscopy (×60 000).

of fibrinogen A alpha gene (FGA) point mutation with the p.E545V variant.

In January 2022, the patient experienced worsening dyspnea, lower-extremity edema, and neuropathic pains. A transthoracic echocardiogram was normal with a left ventricular ejection fraction of 65% and showed no evidence of valvular disease, wall motion abnormalities, or pericardial effusions. A cardiac magnetic resonance imaging (MRI) was performed in February 2022 and showed no evidence of cardiac involvement by amyloidosis. In March 2022, he underwent a peripheral nerve biopsy to evaluate his worsening neuropathic pains. The results were negative for amyloid deposition but showed diabatic neuropathy.

Therapeutic Focus and Assessment

It was concluded that the patient had kidney transplant limited AFib amyloidosis. The patient was managed conservatively

using diuretics, angiotensin receptor blockers, and sodium glucose transport 2 (SGLT2) inhibitors. Weight loss, exercise, and blood glucose control measures were implemented. His last clinic follow-up was in June 2023 when his creatinine was 168.88 μmol/l, and his urine continued to have no proteinuria. Due to the absence of proteinuria, he was judged to have been diagnosed early in the clinical course of his kidney transplant AFib amyloidosis.

Discussion

Renal amyloidosis is characterized by progressive tissue deposition of misfolded proteins that can lead to renal failure. There are multiple types of renal amyloidosis, but the main categories include amyloidosis due to light chains, chronic inflammation, and hereditary causes.[1] AFib amyloidosis of the kidneys is the most common form of hereditary amyloidosis in many countries.[2-4] While AFib amyloidosis is known to recur in kidney transplants,[5,6] we now report a case of AFib amyloidosis in a kidney transplant recipient who was not known to have AFib amyloidosis prior to kidney transplantation.

De novo amyloidosis is the condition when amyloidosis develops after transplantation but had not been known to be present prior to transplantation. *De novo* amyloidosis occurring in the kidney transplant is extremely rare, but few reports have described its occurrence mostly in the context of chronic inflammatory states[7-13] and paraproteinemia.[14-16]

De novo AA amyloidosis of the kidney transplant was described as early as 1979 in a patient with rheumatoid arthritis and chronic infections who died from pancreatitis 5 years after transplantation and whose autopsy showed amyloid AA deposits in the vessel walls of the kidney transplant.[7] Subsequently de novo AA amyloidosis of the kidney transplant was reported in the context of recurrent urinary tract infections, rheumatoid arthritis, ankylosing spondylitis, hepatitis C, pulmonary aspergillosis, and pyoderma gangrenosum.[8-12] Also, *de novo* ALECT2 amyloidosis that occurred 15 years after transplantation was seen in a patient who had repeated episodes of rejection, transplant glomerulopathy, and C1q nephropathy.[13] In these case reports, it was hypothesized that *de novo* AA or de novo ALECT2 amyloidosis in the kidney transplant is likely a long-standing complication of poorly controlled chronic inflammation.

De novo AL amyloidosis of the kidney transplant was described as early as 1998 in a patient who developed nephrotic syndrome 7 years after kidney transplantation.[14] A similar case was reported in 2010 in a patient with proteinuria and kidney transplant failure 5 years after transplantation.[15] Subsequently, a case series of *de novo* AL amyloidosis that included 4 patients was published in 2011 in the *American Journal of Transplantation*.[16] All 4 patients had AL amyloidosis at a minimum of 16 years after transplantation. The diagnoses were proven by kidney transplant and bone marrow biopsies, and all had monoclonal lambda light chains on serum immunofixation. Two of these patients had remission of disease after bone marrow transplantation, and the other two patients died due to AL amyloid. In these reports, it was concluded that AL amyloidosis is an uncommon but serious cause of late-onset proteinuria of the kidney transplant.

In contradistinction to the previously reported forms of *de novo* amyloidosis, our patient is suspected to be a case of *de novo* AFib amyloidosis. The latter is a hereditary disease that is caused by FGA gene mutations on the fourth chromosome,[2-4] which can occur through frameshift, deletion, or substitution mutations. To date, there are at least 9 FGA known mutation variants that are associated with renal amyloidosis, but the precise mechanisms by which they propagate amyloid formation are not completely understood.[3] Our patient had a single nucleotide substitution mutation encoded in p.E545V. This mutation is the most frequently identified variant worldwide and is pathologic for AFib amyloidosis.[3,4] Its mode of inheritance is autosomal dominant with variable penetrance. Genetic testing is required not only to confirm the diagnosis of AFib amyloidosis but also to screen family members for genetic counseling and selection of potential organ donors.[5] Even though AFib amyloidosis is uncommon, recent studies showed that it accounts for 1% of ESKD in the Western World,[4] and it is the most common hereditary renal amyloidosis.[3,5,16,17]

The pathogenesis of FGA gene mutations is due to hepatic production of misfolded fibrinogen proteins that subsequently accumulate in tissues and organs causing amyloid deposits with predilection for the kidneys and nerves. Fibrinogen A alpha chain amyloidosis with renal involvement may manifest in different ways. Clinical presentations vary with respect to age, disease onset, rate of progression, prognosis, and organ involvement.[4,17-20] Patients with an advanced disease usually present with nephrotic range proteinuria, hypertension, and worsening renal function. Some may have a rapid progression to ESKD in 4 to 5 years from the onset of symptoms.[2-5] While AFib amyloidosis has predilection for the kidneys and some investigators have considered it a renal limited disease,[17] others have reported pathologic evidence of widespread systemic involvement.[19] Of interest is that mutations of the FGA gene that cause renal amyloidosis have not been associated with bleeding disorders.

Recurrence of AFib amyloidosis has been well documented after kidney transplantation.[5,6,17,19] Gilmore et al[17] published a report in 2009 on the outcomes of 12 patients from the United Kingdom with AFib amyloidosis who received kidney transplants. Three of them developed allograft failure due to recurrent disease at 5.8, 6.0, and 7.4 years after transplantation. In 2013, the UK National amyloidosis Center reported kidney transplant outcomes of 19 patients with AFib amyloidosis. These patients received a total of 21 kidney transplants, 9 of which were combined liver and kidney transplants (CLKTs).[6] The 5- and 10-year

renal allograft survival rates were 85% and 30% in isolated kidney transplants and were 63% and 31% in the CLKTs. Seven patients with isolated kidney transplants developed a recurrent kidney disease that led to renal allograft loss in three. Despite recurrent disease, the median graft survival for isolated kidney transplants was not statistically different from that of CLKTs due to a much higher postoperative mortality in the CLKTs. In a more recent review from France in 2020, 19 patients with AFib amyloidosis underwent transplantation. Fifteen had isolated kidney transplants, and 4 had CLKTs. In the CLKTs, no recurrent disease was seen. In the isolated kidney transplant patients, the severity of recurrence correlated with the underlying genetic abnormality. In this series, when the E526V point mutation was present, recurrence of AFib amyloidosis in the kidney graft was 22%; however, it was 83% with a non-E526V variant (R554L or frameshift). Also, with the E526V point mutation, renal allograft loss was much less frequent (33% vs 100%).

It is interesting that our patient never carried the diagnosis of AFib amyloidosis prior to transplantation nor had known family history of such disease. He had several traditional risk factors for kidney disease, and his history, comorbidities, and age of presentation with ESKD were highly suspicious for diabetic kidney disease from type 2 diabetes mellitus that was further complicated by hypertension and obesity. Hence, when AFib amyloidosis was discovered on his kidney transplant biopsy, we suspected that it is likely to be a case of *de novo* AFib amyloidosis of the kidney transplant. Nevertheless, we cannot totally exclude the possibility that the diagnosis of AFib amyloidosis of his native kidneys could have been missed because his native kidneys were not biopsied, and this is the main critique of this article.

The treatment of patients with AFib amyloidosis in native or transplanted kidneys who have not reached ESKD is largely supportive care. Early liver transplantation is considered curative. The patients with ESKD are advised to undergo simultaneous kidney-liver transplantation.[18,19] Such combined organ transplantation has been shown to halt disease progression and prevent recurrence.[18-20] Our patient had no clinically detectable proteinuria, so he was judged to have been diagnosed early in the course of AFib amyloidosis of his kidney transplant. Also, the kidney transplant is the only organ involved in his case, and he is being treated conservatively. Liver transplantation was discussed with the patient, but it was not considered since it would carry a high mortality risk due to his advancing age, obesity, uncontrolled type 2 diabetes mellitus, and background coronary artery disease.

In conclusion, we present a kidney transplant patient who was discovered to have AFib amyloidosis of his kidney transplant. Because he was not known to have AFib amyloidosis prior to kidney transplantation, we argue that his case could be considered a case of *de novo* AFib amyloidosis in kidney transplantation. In discussing this case, we make the following important points: (1) illustrate the sequence of steps that were undertaken to reach the diagnosis of AFib amyloidosis; (2) highlight that while AFib renal amyloidosis is uncommon, it is the most common hereditary renal amyloidosis; (3) emphasize that AFib amyloidosis carries a high rate of recurrence in isolated kidney transplants, but prevention of recurrence requires CLKTs; and (4) raise awareness of the possibility of AFib renal amyloidosis in kidney transplant patients suffering from unexplained proteinuria or worsening kidney function.

Ethics Approval and Consent to Participate

This is a case report with no associated patient identifiers. The patient was treated based on standard of care. The patient has provided informed consent for this publication. The patient's privacy in this report was respected by eliminating any personal identifiers, and in compliance with the declaration of Helsinki.

Consent for Publication

The patient was made aware of the intent to publish his case as a teaching case report. He agreed and provided a written consent.

Availability of Data and Materials

All the clinical, laboratory, genetic testing, and pathology data related to this report are available on file in the clinical record of the patient and the authors would be able to provide access to such data upon appropriate request and in compliance with privacy regulations.

Acknowledgments

The authors thank Dr. Angelina Edwards, Director of the Houston Methodist Fellowship Program, for her support in this work.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: Renal Research, Inc., a nonprofit organization dedicated for kidney research.

ORCID iD

George Nassar https://orcid.org/0000-0002-6582-5519

References

1. Gupta N, Kaur H, Wajid S. Renal amyloidosis: an update on diagnosis and pathogenesis. *Protoplasma*. 2020;257(5):1259-1276.
2. Chapman J, Dogan A. Fibrinogen alpha amyloidosis: insights from proteomics. *Expert Rev Proteomics*. 2019;16(9):783-793.

3. Rowczenio D, Stensland M, de Souza GA, et al. Renal amyloidosis associated with 5 novel variants in the fibrinogen alpha chain protein. *Kidney Int Rep*. 2016;2(3):461-469.
4. Tavares I, Oliveira JP, Pinho A, et al. Unrecognized fibrinogen A alpha chain amyloidosis. results from targeted gene testing. *Am J Kidney Dis*. 2017;70(2):235-243.
5. Feitosa VA, Ferreira FT, Neves PDMM, et al. Post-transplantation recurrence of fibrinogen A-α amyloidosis. *Kidney Int Rep*. 2021;6(1):234-238.
6. Pinney JH, Lachmann HJ, Sattianayagam PT, et al. Renal transplantation in systemic amyloidosis-importance of amyloid fibril type and precursor protein abundance. *Am J Transplant*. 2013;13(2):433-441.
7. Light PD, Hall-Craggs M. Amyloid depositions in a renal allograft in a case of amyloidosis secondary to rheumatoid arthritis. *Am J Med*. 1979;66(3):532-536.
8. Harrison KL, Alpers CE, Davis CL. *De novo* amyloidosis in a renal allograft: a case report and review the literature. *Am J Kidney Dis*. 1993;22(3):468-476.
9. Rojas R, Josephson MA, Chang A, Meehan S. AA amyloidosis in the renal allograft: a report of two cases and review of the literature. *Clin Kidney J*. 2012;5(2):146-149.
10. Peces R, Ablanedo P, Seco M. Amyloidosis associated with chronic granulomatous disease in a patient with a renal transplant and recurrent urinary tract infections. *Nefrologia*. 2002;22(5):486-491.
11. Yilmaz S, Ozcakar Z, Bulum B, et al. *De novo* amyloidosis in a renal transplant patient. *Pediatr Transplant*. 2014;18(8):E259-E261.
12. Ortiz MJ, Levy F, Abaigar P, et al. Acute kidney transplant failure from *de novo* aa amyloidosis in a patient with pyoderma gangrenosum. *Nefrologia*. 2010;30(4):482-484.
13. Shamir ER, Lee MM, Walavalkar V. *De novo* leukocyte chemotactic factor 2 amyloidosis in a pediatric renal allograft, 15 years post-transplantations. *Pediatr Transplant*. 2019:23:e13371.
14. Le QC, Wood T, Alpers C. *De novo* AL amyloid in a renal allograft. *Am J Nephrol*. 1998;18(1):67-70.
15. Chen DJ, Jiang H, Yang H, et al. Unusual cause of proteinuria and re-renal failure after kidney transplantation; *De novo* localized AL amyloidosis in renal allograft. *Int Urol Nephrol*. 2010;42(2):507-511.
16. Qian Q, Nasr SH, Fidler ME, Cornell LD, Sethi S. *De novo* AL amyloidosis in the kidney allograft. *Am J Transplant*. 2011;11:601-661.
17. Gillmore JD. Diagnosis, pathogenesis, treatment, and prognosis of hereditary fibrinogen A alpha-chain amyloidosis. *J Am Soc Nephrol*. 2009;20(2):444-451.
18. Stangou AJ, Banner NR, Hendry BM, et al. Hereditary fibrinogen A alpha-chain amyloidosis: phenotypic characterization of a systemic disease and the role of liver transplantation. *Blood*. 2010;115(15):2998-3007.
19. Gillmore JD, Booth DR, Rela M, et al. Curative hepatorenal transplantation in systemic amyloidosis caused by the Glu526Val fibrinogen alpha-chain variant in an English family. *QJM*. 2000;93(5):269-275.
20. Meyer L, Ulrich M, Ducloux D, et al. Organ transplantation in hereditary fibrinogen A alpha-chain amyloidosis: a case series of French patients. *Am J Kidney Dis*. 2020;76(3):384-391.