10.5152/turkjnephrol.2021.4596

Case Report

Turkish Journal of Nephrology

Early Post-transplant Recurrence of Amyloidosis in a Patient with Familial Mediterranean Fever

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ABSTRACT

Familial Mediterranean fever is the most common hereditary auto-inflammatory disease characterized by a recurrent attack of fever and serositis. Untreated patients frequently develop AA type of amyloidosis which results in end-stage kidney disease (ESKD). Renal transplantation is the preferred renal replacement modality for these patients. Recurrence of amyloidosis in the graft is possible but generally requires several years after transplantation. We herein present a patient with an unexpected early recurrence of AA type amyloidosis secondary to familial Mediterranean fever in graft kidney despite regular colchicine prophylaxis.

Keywords: AA type amyloidosis, familial Mediterranean fever, recurrence, renal transplantation

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Received: September 1, 2020 **Accepted:** November 19, 2020

Cite this article as: Aral Özbek D, Sıla Koç N, Sağlam A, Yildirim T, Rahmi Yilmaz Ş, Erdem Y. Early post-transplant recurrence of amyloidosis in a patient with familial mediterranean fever. *Turk J Nephrol.* 2021; 30(2): 179-182.

INTRODUCTION

Familial Mediterranean fever (FMF) is the prototype of hereditary auto-inflammatory syndromes that presents with recurrent attacks of fever and serositis. Disease is predominantly seen in the Mediterranean populations, such as Turks, Arabs, Jews, and Armenians.[1] Amyloidosis is the most debilitating complication of FMF, which is defined as a secondary AA type amyloidosis that has multisystemic involvement, but most commonly affects kidneys and presents with features of nephrotic syndrome.[2] Colchicine is still the first-line treatment of FMF while biologic agents have emerged in twenty-first century for colchicine-resistant or intolerant patients.[3] Renal transplantation has been successfully performed for end-stage kidney disease (ESKD) due to AA type amyloidosis secondary to FMF, with recurrence of amyloidosis can be seen late after transplantation and may result in graft failure. We herein present a case presenting with recurrence of AA amyloidosis in transplanted kidney secondary to FMF within the first year of transplantation, which is one of the earliest recurrences under regular colchicine treatment to be reported to our knowledge.

CASE REPORT

A 3-year-old male patient was admitted to the hospital with recurrent attacks of abdominal pain and fever and diagnosed as FMF that was confirmed by genetic test homozygote for M694V in MEFV gene. His father also had a previous diagnosis of FMF. Colchicine treatment was started and the daily dose was gradually increased due to recurrent FMF flares and increased levels of inflammatory markers. The patient had no proteinuria and his glomerular filtration rate (GFR, estimated with CKD-EPI formula) was normal at the time of diagnosis; however, he did not use colchicine and admit his follow-up admissions on a regular basis and attacks continued. The patient was lost to follow-up for 7 years, until he was admitted again with generalized edema at the age of 18. On admission, the serum creatinine level was 6.52 mg/dL, GFR was 11 mL/min, and 24-h urinary protein was 9.6 g. Kidney biopsy revealed

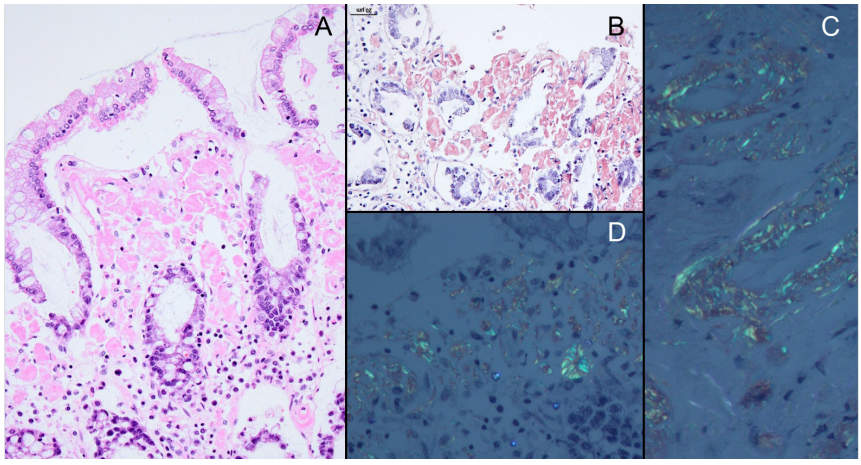

Figure 1. a-d. Globular deposition of amorphous eosinophilic material within the lamina propria (A- H&E) which is congophilic (B) and shows apple-green birefringence under polarized microscopy (C), consistent with amyloid. The deposition is also present along the submucosal vessel walls (D- polarized microscopy).

AA type amyloidosis and he was diagnosed as ESKD secondary to amyloidosis.

Pre-emptive renal transplantation was planned from his mother, who had no known disease and had normal levels of GFR, 24-h proteinuria, and inflammatory markers. She also had no history of recurrent flares with fever/serositis that might be interpreted as FMF. Both Class I and II Panel Reactive Antigen and Lymphocyte Cross-Match tests were negative and renal transplantation was performed without any complication. Creatinine level decreased to 0.9 mg/dL after transplantation and the patient was started on prednisolone, mycophenolate mofetil, and tacrolimus. Tacrolimus was switched to cyclosporine due to hyperglycemia before discharge. Colchicine treatment was also started at a dose of 1 mg/day.

The post-transplant course was uneventful until 11 months after transplantation when the patient was admitted to the hospital with fever, diarrhea, and constitutional symptoms including weight loss and malaise. Laboratory analysis revealed a serum creatinine level of 2.26 mg/dL, serum albumin level of 2.86 g/dL, and GFR of 37.51 mL/min with 24-h protein excretion of 7.6 g/day. C-reactive protein (CRP) level was increased to 7.27 mg/dL. His cyclosporine level was in the target range (C_2 level of 584 ng/mL). He had a urinary tract infection that was successfully treated. He also reported diarrhea. Stool microscopy, bacterial stool culture, examination of stool for ova and parasites, assay for Clostridium Difficile toxin, and serum cytomegalovirus load were negative. Fibersigmoidoscopic biopsy revealed extensive amyloid deposition that reacted positively with Congo-Red stain (Figure 1). Since there was no improvement in GFR during hospitalization a renal biopsy was performed.

Pathologic examination of the graft biopsy showed extensive amyloid deposition in all compartments of the kidney such as arterioles, glomerular and tubular basement membranes, and interstitium. Congo-Red staining was positive and immunohistochemical staining was also positive for amyloid and negative for immunoglobulins. Anti-C4d staining was negative. Active and chronic tubulointerstitial inflammation with lymphocytic and eosinophilic infiltrates were also accompanying amyloid deposits (Figure 2).

The patient was diagnosed with recurrence of AA amyloidosis due to FMF. The patient insisted that he used colchicine regularly after transplantation. A retrospective review of the results of laboratory tests revealed erythrocyte sedimentation rate (ESR), CRP, and fibrinogen levels above the upper limit during the post-transplant follow-up. Anti-interleukin-1 (IL-1) antagonist, anakinra, was added to the treatment and the patient was discharged with a serum creatinine level of 1.1 mg/dL.

Main Points

The patients with FMF develop ESKD due to amyloidosis. Recurrence of amyloidosis may occur in renal transplant recipients with FMF. We present the early relapse of amyloidosis in our case. Therefore, amyloidosis should be considered in the presence of proteinuria and high creatinine in transplant patients, even in the early period.

DISCUSSION

Renal transplantation has been performed for a long period of time in AA type amyloidosis secondary to FMF.[4] Data about the outcome of recipients is still inconclusive, as some of the recent studies with large sample sizes and long-term follow-up

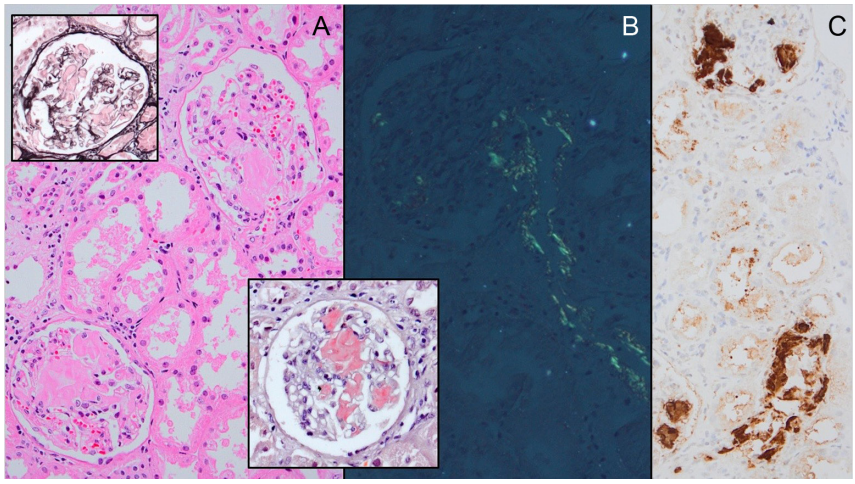

Figure 2. a-c. (A) Glomeruli showing a nodular expansion of the mesangium with amorphous eosinophilic material which is argyrophobic with Jones Methamine Silver stain (upper inset) and congophilic (inset lower center), consistent with amyloid. (B) The material shows apple-green birefringence under polarized microscopy. (C) Immunohistochemistry demonstrating positivity with anti-amyloid A protein.

periods showed increased mortality and allograft failure especially on the short-term[5,6]; while others not.[7,8] As an etiology of graft failure and mortality, recurrence of amyloidosis has been an infrequent complication in most of these and other studies with reported incidences as low as 4.3%[8]; but reported as high as 25.9% in a single-center study from Turkey.[6] Recurrence of amyloidosis commonly presents as proteinuria that can be in the nephrotic range and an increase in creatinine level and graft failure may develop.

Recurrence of amyloidosis due to FMF has usually been reported as a late complication that can be seen even after 19 years post-transplant.[9] In most of the studies no routine post-transplant biopsy data is available, which did not make it possible to obtain the exact data about time to recurrence. On the basis of clinical follow-up, the earliest biopsy-proven renal amyloid recurrences due to FMF that have been reported diagnosed at 6.5th months post-transplant; of which information about colchicine treatment was absent.[5]

The risk of recurrence for AA type amyloidosis after renal transplantation, in general, depends on the type of the primary disease.[10] On the aspect of FMF; continuing colchicine after transplantation decreases the risk of recurrence of amyloidosis.[11,12] As with other AA type amyloidosis etiologies, the activity of the primary disease can increase the risk of recurrence after transplantation.[6,10] Our patient had also gastrointestinal amyloidosis which can be considered as marker of high disease activity.[13]

Being under treatment with colchicine does not necessarily imply that amyloidosis will be prevented. High levels of acute-phase proteins may predict the development of amyloidosis. For this reason, checking acute-phase reactants regularly and switching to novel treatments such as anakinra or canakinumab should be considered in patients with high levels of inflammatory markers. Another strategy to prevent the development of recurrent amyloidosis in the post-transplant period is taking a good history of the pretransplant course of the disease. Development of amyloidosis despite regular colchicine treatment before transplantation may be a clue for colchicine resistance and these patients should probably be started anti-IL-1 treatments soon after transplantation.

In conclusion, recurrence of amyloidosis should always be ruled out in renal transplant recipients with a primary diagnosis of FMF and amyloidosis in case of de novo proteinuria and/or increase in creatinine, especially for patients with high disease activity. Our case presents one of the earliest amyloidosis recurrences, in spite of colchicine treatment, so the time from transplantation or being under regular colchicine treatment solely cannot rule of recurrence amyloidosis.

Informed Consent: N/A.

Peer-review: Externally- peer reviewed.

Author Contributions: Concept – D.A.Ö., N.S.K., T.Y.; Design - D.A.Ö., N.S.K., T.Y.; Supervision - T.Y, Ş.R.Y. ,Y.E.; Resource - D.A.Ö., N.S.K., T.Y.; A.S.; Materials - D.A.Ö., N.S.K., T.Y., A.S.; Data Collection and/or Processing - D.A.Ö., N.S.K., T.Y.; Analysis and/or Interpretation - D.A.Ö., N.S.K., T.Y.; Literature Search - D.A.Ö., N.S.K., T.Y.; Writing - D.A.Ö., N.S.K.; Critical Reviews - T.Y, Ş.R.Y., Y.E.

Conflict of Interest: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

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