A CASE REPORT OF AA AMYLOIDOSIS ASSOCIATED WITH FAMILIAL PERIODIC FEVER SYNDROME DIAGNOSED AFTER KIDNEY TRANSPLANTATION: NEVER SAY NEVER

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Abstract

Recurrent or “de novo” AA amyloidosis in the renal allograft is rarely described. We describe a case of severe nephrotic syndrome in a recipient of a kidney graft with previous diagnosis of polycystic nephropathy whose etiological disease was diagnosed as AA amyloidosis possibly TNF receptor-associated periodic syndrome (TRAPS) related only after the renal transplantation. TRAPS is a rare hereditary inflammatory disease never reported as a de novo diagnosis in the transplantation setting, to the best of our knowledge. Biopsy of the renal graft, indicated for the recent onset of heavy proteinuria, and genetic investigation were the clue for diagnosis.

Introduction

AA amyloidosis is a disorder characterized by extracellular deposition of amyloid A protein, derived from the precursor serum amyloid A (SAA), in the form of fibrils, which leads to a progressive organ dysfunction. SAA is an acute-phase protein produced by hepatocytes in response to inflammation. Kidney transplant is an accepted treatment for patients with renal involvement and end-stage kidney disease. Recurrent AA amyloidosis is infrequent and graft loss caused by this condition is uncommon (1). The first occurrence of "de novo" secondary amyloidosis in a kidney transplant recipient was described in 1993 (2). Since then, few other cases have been reported; an underlying chronic inflammatory disease was recognised in most of these cases. We report the case of a patients suffering from polycystic kidney disease in whom a diagnosis of AA amyloidosis was performed "de novo" in the renal allograft, with rapid failure of graft function. Lacking any evidence for underlying inflammatory disease, a genetic screening was performed. Only when subsequent investigations showed one of the low penetrance mutations related with the TNF Receptor-Associated Periodic Syndrome (TRAPS), a quite rare hereditary inflammatory disorder, could the association be suspected. Colchicine therapy, recognized as an effective drug for treatment and prevention of familial Mediterranean fever (FMF) related amyloidosis, was successfully used in our patient to treat symptoms and complications of the inflammatory syndrome.

Case report

We report the case of a 50-year-old caucasian man from Southern Italy, affected with polycystic kidney disease, who developed a picture consistent with secondary amyloidosis in a kidney allograft. The diagnosis of polycystic kidney disease was made in 1999. No other significant comorbidity was reported. Hemodialysis was initiated in 2007 and in December 2009 he underwent an uneventful kidney transplantation from a deceased donor in another Italian transplantation center. He was discharged on triple immunosuppressive therapy (cyclosporine, mycophenolate mofetil and steroids) with a good renal function (sCr 1.1 mg/dl, proteinuria 0.1 g/day). In the following months one episode

of Cytomegalic infection and some episodes of urinary tract infections were successfully treated. In June 2011, because of an episode of abdominal pain of unknown cause, associated with mild myalgia and arthralgia, the patient was hospitalized in our center. His renal function was worsened (sCr 4.9 mg/dl) and a nephrotic range proteinuria was detected (8 g/day). No serum and urinary monoclonal components were found, immunological tests (rheumatoid factor, antinuclear, double strand anti-DNA and anti-neutrophil cytoplasmatic antibodies, cryoglobulins, IgG, IgA, IgM and C4 levels) were negative apart from hypocomplementemia C3. When clinical and nephrological conditions were improved by means of albumin infusions and diuretic therapy, the patient underwent a renal biopsy. The sample submitted contained 17 glomeruli. All glomeruli showed mesangial periodic acid-Schiff-positive amorphous material, also present in the vessels, in the tubuli and focally in the interstitium. This material stained Congo red positive and demonstrated apple-green birefringence under polarized light. Immunofluorescence microscopy was negative for *K* and λ light chains and positive for P and A components. The diagnosis was in favour of AA amyloidosis. Laboratory and instrumental investigations were performed in order to exclude chronic inflammatory diseases and infections even in the absence of suggestive clinical signs (during the hospitalization the patient became completely asymptomatic for inflammation), including a total body PET, the Quantiferon test, the screening for Inflammatory Bowel Diseases and Celiac Disease. All tests were negative. Serum amyloid A (SAA) test ranged between 40-60 mg/l (normal values < 6.4 mg/l). Investigation of the *MEFV* gene, encoding for marenostrin, was found negative for the most common mutations in the mediterranean area (mutations analyzed: E148Q, P369S, F479L, M680I (G/C), M680I (G/A), I692del, M694V, M694I, K695R, V726A, A744S, R761H; detection rate 85%). So we decided to perform investigations for other genetic autoinflammatory syndromes (table 1). Meanwhile, the right native kidney was removed to rule out any infection or malignancies (on the basis of flank pain and CT imaging) and the intestinal mucosa was biopsied because of a severe hemorrhagic colitis (which was histologically demonstrated as CMV related). In both specimens AA amyloidosis was demonstrated. sCr initially decreased up to 2.5 mg/dl but subsequently worsened again and proteinuria reached the value of 20 g/day. Antiproteinuric therapy (ACE inhibitors) and also the increase of cyclosporine dosage with the aim of procuring a nephrotoxic effect both failed in obtaining an improvement of proteinuria. Hemodialysis

was started in December 2011. The immunosuppressive therapy was reduced and the graft was not removed. In the same month a repeated echocardiography demonstrated the onset of cardiac involvement (thickening and increased echogenicity of the interventricular septum), which was absent in a previously performed test. A part from the need to resume the dialytic treatment for the worsening renal function and uremic symptoms, a therapy focused on suppressing or reducing the inflammatory status was considered, particularly in view of the cardiac involvement. Eprosidate, recently proposed as a modality of interrupting amyloid fibril deposition (3) but not yet available in our country, could not be obtained, not even for compassionate use in our patient, in view of the severe renal impairment. So we decided to use colchicine at the dose of 0.5 mg/day to treat the inflammation syndrome. When we started with the drug, hemodialysis had already been initiated. The drug was well tolerated and after nine months of therapy the patient is doing well, has a good quality of life without any new sign of AA amyloidosis related systemic complications. His SAA is persistently within the normal range (1.4 mg/l at the last determination). Two months after the replacement of dialysis we obtained the results of the genetic tests that detected the low penetrance mutation R92Q on *TNFRSF1A* gene, considered a risk factor for TNF receptor-associated periodic syndrome (TRAPS) (4-6). So we opted for a case of AA amyloidosis in a renal allograft recipient TRAPS associated, to the best of our knowledge. The patient's follow-up is now being performed by a reference center for the disease, where further studies on *MEVF* gene will be performed.

Discussion

The most frequent complication of AA Amyloidosis is renal disease characterized by nephrotic syndrome and a progressive decline of renal function. Kidney transplant can be performed in hemodialysis patients with renal involvement although the importance of a careful screening and management of both cardiovascular and infectious complications to reduce the high risk of mortality have been recently stressed (7). Recurrent AA amyloidosis in the renal allograft has been documented in patients with ankylosing spondylitis, rheumatoid arthritis, Familial Mediterranean Fever (FMF), Crohn disease, chronic pyelonephritis and tubercolosis (8). De novo AA amyloidosis has rarely been reported. We can assume that we were describing a case of AA amyloidosis with acutely developed

signs and symptoms, because of the physiological values of proteinuria before dialysis and in the early post transplantation course and because of the rate of progression of the amyloidotic disease. The clinical course in our patient was particularly aggressive with a rapid decline in renal function and the progressive appearance of signs of systemic involvement in spite of minimal clinical symptoms of a chronic inflammatory syndrome. Only the biopsy of the renal graft allowed the identification of an unexpected disorder leading us to a more appropriate etiological and diagnostic process. On the basis of the second line genetic investigation, AA amyloidosis was presumed to be related to TRAPS, a rare hereditary inflammatory disease never reported as a de novo diagnosis in the transplantation setting, to the best of our knowledge. TRAPS is caused by autosomal-dominant mutations in *TNFRSF1A*, the gene that encodes for the tumor necrosis factor receptor superfamily 1 A, the main cell surface receptor for TNF. The mutations of this gene result in an upregulation of the inflammatory responses. Onset is usually in childhood; clinical manifestations include fever, migratory erythematous macular rashes, periorbital edema, myalgia, arthralgia and abdominal pain of relapsing and remitting nature (4). "A posteriori", either the myalgia or the arthralgia and the abdominal pain could be interpreted as TRAPS related symptoms. Also some previous episodes of transitory cutaneous rashes of unexplained nature were reported by the patient at an in-depth and targeted questioning. Amyloidosis is reported in 15% of cases of TRAPS (5). Our patient shows that this complication may be the first manifestation of TRAPS, even in the absence of clear clinical symptoms of inflammation. The delayed diagnosis of the rare genetic disorder is not uncommon. The case can be considered unusual since only after the onset of the heavy proteinuria, due to the occurrence of AA amyloidosis in the graft, the affection could be thoroughly investigated and the demonstration of the other sites of AA fibril deposition could be sought. Morever, the association between AA amyloidosis and TRAPS was acquired only thanks to the "second line" genetic investigation and not on the basis of a clinical suspicion. The TRAPS related symptoms were very mild, no recurrent fever attack was reported by the patient in his medical history. When histological and immunohistochemical analysis demostrate an AA amyloidosis, and particularly in absence of significant infective/inflammatory disease, a thorough genetic investigation should be performed. Although colchicine therapy is validated only for the treatment of FMF, in our patient, so far, it has proved to be effective in controlling the chronic inflammatory state. Although the response

to colchicine and AA amyloidosis are two sufficient criteria for the clinical diagnosis of FMF (table 2) (9), we believe that our patient's symptoms, the late onset of the disease and the genetic alteration are more indicative of a TRAPS. A total of 114 sequence variants of the *TNFRSF 1A* have been recorded so far, of which 75 are associated with a TRAPS phenotype (10). The status of R92Q sequence has not been fully determined, but appears rather as an incomplete penetrance mutation suggesting that additional pathogenetic mechanism could be involved. We wonder if the mild infections, that the patient developed only after the kidney transplantation, could have acted as exogenous environmental factors triggering the TRAPS symptoms in a condition of a genetic predisposition. We are aware that in the last few years three different drugs have been tested and used for treatment of TRAPS related sumptoms: etanercept, anakinra and most recently canakinumab (11-13). None of these drugs was considered for our patient during the hospitalization in our unit because the evidence in favour of the genetic disease was obtained afterwards. In conclusion, we report a case of severe nephrotic syndrome in a transplanted patient with previous diagnosis of polycystic kidney disease whose etiological disease was diagnosed as AA amyloidosis possibly TRAPS associated. The renal biopsy and a genetic investigation were the clue for diagnosis, of outmost importance also in view of the option of retransplantation, although this has not yet been required by the patient. Thanks to colchicine therapy, we have obtained, so far, good results in controlling the underlying inflammatory state, so improving also the patient's quality of life, opening the possibility of a retransplant option.

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Table 1: PERIODIC FEVERS				
DISEASE	**GENE CHROMOSOME**	**PROTEIN**	**TRANSMISSION**	**CLINICAL FEATURES**
Familial mediterranean fever (FMF)	MEVF 16p13.3	Pyryn	Autosomal recessive	Short duration of fever episodes (1-2 days). Serositis and arthritis. Erysipelas-like erythema. High incidence of renal amyloidosis in untreated patients.
TNF receptor associated periodic syndrome	TNFRSF1A 12p13	P55 THF receptor	Autosomal dominant	Prolonged fever episodes (1-3 weeks). Abdominal pain. Skin rashes. Myalgias and arthritis. Orbital oedema. Incidence of renal amyloidosis: 15%.
Mevalonate kinase deficiency	MVK 12q24	Mevalonate kinase	Autosomal recessive	Duration of fever episodes: 4-5 days. Abdominal pain, vomiting and diarrhoea. Splenomegaly. Amyloidosis is rare.
NALP12-associated periodic Fever	NALP12 19q13	NALP12	Autosomal dominant	Periodic fever after cold exposure. Hearing loss.

Table 2: Tel-Hashomer diagnostic criteria for Familial Mediterranean Fever (FMF)	
MAJOR CRITERIA	**MINOR CRITERIA**
Recurrent fever episodes and serositis	Recurrent fever episodes
Evidence of AA amyloidosis	Erysipelas-like erythema
Good response to colchicine	Family history for FMF (1° grade)
Diagnosis with 2 major criteria or 1 major criteria + 2 minor criteria. **Possible diagnosis** with 1 major criteria and 1 minor criteria	