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Late Diagnosis of Familial Mediterranean Fever in Kidney Transplant Recipients

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Abstract

Introduction: Familial Mediterranean Fever (FMF) causing AA amyloidosis and chronic renal failure is also called recurrent polyserositis. Diagnosis of FMF is established by clinical signs and sometimes by genetic analysis for MEFV mutations.

Case Presentation: We presented four cases of kidney transplantation recipients (KTrs). Interestingly, FMF was diagnosed following episodes of acute renal failure, abdominal pain, and/or fever in these KTrs. When colchicine was added to their standard therapy, these events did not develop.

Conclusion: Therefore, in cases with unknown etiologies of fever, abdominal pain, and even acute renal failure in KTrs, FMF should also be considered, particularly in certain geographic areas and ethnic groups.

Keywords: Familial mediterranean fever, renal transplantation, acute renal failure

Introduction

Familial Mediterranean fever (FMF) is also called recurrent polyserositis. The prominent features of FMF include brief recurrent episodes of peritonitis, pleuritis and arthritis, usually with accompanying fever. FMF is most common among ethnic groups from the Mediterranean region, notably people of Armenian, Arab, Turkish, Iraqi Jewish, and North African Jewish ancestry (1). The disorder is inherited in an autosomal recessive fashion. Of all patients with FMF, 50-60% are younger than 10 years old, 80-95% are younger than 20 years old, and 5-10% are over 20 years old at onset. Onset in persons over 40 years old is rare. Colchicine is very effective in preventing familial Mediterranean fever (FMF) attacks and development of amyloidosis. Amyloidosis is diagnosed in 90% of patients when they are still not treated by around 40 years old (2). In this paper, we reported on four cases of kidney transplantation recipients (KTrs). FMF was diagnosed following recurrent (several times) hospitalizations for acute renal failure, fever and/or abdominal pain in these KTrs.

Case-1. A 35-year-old female KTr admitted to our emergency department with disorders of consciousness, seizures and hypertension. In

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the medical history, there was hospitalization several times for diagnosis of chronic pyelonephritis, hypertension and epilepsia since she was 8 years old. Continuous ambulatory peritoneal dialysis (CAPD) was begun for chronic kidney disease (CKD) stage-V and she had been hospitalized two times because of abdominal pain and treated for peritonitis for a one-year period. Subsequently, a kidney transplant was performed from a deceased donor. She was treated with a triple immunosuppressive treatment consisting of tacrolimus, mycophenolate mofetil and methylprednisolone. She was hospitalized because of generalized abdominal pain, diarrhea, and arthralgia during posttransplant period two times. Biochemical, microbiological and immunological tests, radiological examination including tomography of thorax and abdomen and upper and lower gastrointestinal endoscopy did not yield a possible explanation for the abdominal pain. At the last hospitalization, genetic testing revealed a homozygous mutation of the Mediterranean Fever (MEFV) gene. With addition of colchicine to her standard treatment (2-3x0.5mg/day), there was no abdominal pain or other symptoms or adverse events developing related to colchicine. Under treatment with colchicine and triple immunosuppressives, she was well and her levels of BUN, creatinine and proteinuria were 20 mg/dL, 1.79 mg/dL and negative, respectively, in the 11th year of her transplantation.

Case-2. A male KTr was hospitalized in the general surgery clinic for suspicion of ileus with severe abdominal pain and vomiting. He was followed in our outpatient clinic as a KTr. Before transplantation, he was hospitalized several times in Russia because of abdominal pain, high fever and malaise, without any diagnosis. After three months of hemodialysis treatment for CKD stage V with unknown etiology, kidney transplantation from his sister was performed at another hospital. During the post-transplant period he was hospitalized for paresis on the left side and speech disorder secondary to acute infarct in the left temporoparietal area. In the post-transplant first year he was hospitalized in the general surgery clinic at our hospital because of generalized abdominal pain.

Abdominal pain regressed spontaneously and he was discharged without diagnosis. Due to recurrent abdominal pain lasting 1-2 days occurring 1-2 times every month, a diagnosis of FMF was confirmed with genetic analysis. Colchicine was added to the immunosuppressive drugs. Family history was negative for FMF but his nephew was positive for the FMF gene mutation. The patient was treated with triple immunosuppressive treatment consisting of tacrolimus (target level of Co 5-7 ng/ml), azathioprine (100 mg/day) and methylprednisolone (5mg/day), colchicine (4x0.5 mg /day) and phenytoin (3x100 mg/day). In the 5th year of renal transplantation, his last test was as follows: BUN 14 mg/dL, creatinine 1.21 mg/dL and urine analysis was protein negative.

Case-3. A 22-year-old KTr female admitted to our clinic for generalized abdominal pain, chills, shivering, fever and acute renal failure. At that time, she was a kidney transplant receiver for 3 years. During this period she was hospitalized four times because of similar symptoms. All microbiological tests and radiological examinations were negative. Fever and renal dysfunction improved after empirical antibiotic treatment. At the last hospitalization, she had similar abdominal pain

lasting 2-3 days and fever of around 39°C. Arthritis and chest pain were not found. Her laboratory tests were as follows: leukocyte count 32,000/mm^3, serum C-reactive protein (CRP) 32.6 mg/dl, erythrocyte sedimentation rate 67 mm/h and creatinine 4.33 mg/dL. Urine analysis was normal. No ileus, perforation or other pathologies were found on radiological examinations including direct graphics, ultrasonography and computerized tomography. Genetic testing for an FMF mutation was negative, however the patient was diagnosed as having FMF considering the significant benefit of colchicine treatment. Intravenous fluids and oral colchicine resulted in improvement of all symptoms and renal dysfunction. After beginning colchicine, it was observed that the number and duration of abdominal pain episodes and high fever clearly decreased. Following a normal pregnancy, a baby was delivered under the treatment of tacrolimus, azathioprine, methylprednisolone and colchicine. At the sixth year of kidney transplantation, the last tests were: BUN 12 mg/dL, creatinine 0.91 mg/dL and urine analysis was protein negative, with the

Table-1: Characteristics of all patients.

Cases	Case-1	Case-2	Case-3	Case-4
Renal Transplantation Number	1	1	1	1
Primary Renal Disease	Chronic Pyelonephritis	Solitary Kidney	Unknown	Unknown
Age at diagnosis of CKD	15	32	11	Unknown
Comorbid diseases				
HT	(-)	(+)	(-)	(-)
Epilepsia	+	(-)	(-)	(-)
Cerebrovascular accident	(-)	(+)	(-)	(-)
Duration of dialysis	1 year	3 month	5 year	(-)
Donor sources	Deceased-Donor	Living Donor	Living Donor	Living Donor
Causes of hospitalization before FMF diagnosis	Abdominal Pain, Diarrhea, Nausea, Arthralgia	Abdominal Pain, Diarrhea, Fever, Weakness	Abdominal Pain Fever, Acute Kidney Failure	Abdominal Pain
Age at diagnosis of FMF	33 years	38 years	21 years	Not evaluated
Duration of KT before FMF diagnosis (years)	7	3	5	Not evaluated
Positive FMF genetic test	(+)	(+)	(-)	(+)
At last follow-up				
Duration of KT (years)	11	5	8	4
BUN/creatinine (mg/dL)	20/1.79	14/1.21	42/2.7	9/0.85
Proteinuria	(-)	(-)	(++)	(-)
Medicines	1, 2, 3, 4 carbamazepine	1, 5, 3, 4 phenitoin	1, 5, 3, 4	1, 2, 3, 4

Abbreviations: KT: Kidney Transplantation, BUN: Blood Urea Nitrogen, MMF: Mycophenolate Mofetil, 1: Tacrolimus, 2: MMF, 3: Colchicine, 4: Prednisolone, 5: Azathioprine

patient using colchicine 3x1 tb. She was lost to follow-up for almost two years. On the last visit her levels of BUN/creatinine were 42 mg/dL/2.7 mg/dl at the 8th transplantation year.

Case-4. A twenty-nine year-old KTr female was diagnosed as having FMF after being tested because of abdominal pain attacks during the post-transplant period. Four years ago she received a kidney transplantation from a living related donor. After adding colchicine (3x0.5 mg/day), abdominal pain attacks decreased significantly. Currently, the patient is being treated with triplet immunosuppressive treatment consisting of tacrolimus, mycophenolate mofetil and prednisolone, and colchicine. In 4th year of post-transplantation, the last tests were BUN 9 mg/dL, creatinine 0.85 mg/dL and negative proteinuria.

Discussion

Familial Mediterranean Fever (FMF) is an autosomal recessive disorder characterized by recurrent bouts of fever and peritonitis, sometimes with pleuritis, skin lesions, arthritis, and, very rarely, pericarditis (3,4). Renal amyloidosis may develop, sometimes leading to renal failure. People with genetic origins in the Mediterranean basin are more frequently affected than other ethnic groups. Diagnosis is largely clinical, although genetic testing is available. Treatment with prophylactic colchicine prevents acute attacks as well as amyloidosis in almost all patient. Prognosis is excellent with colchicine treatment. During FMF attacks, peritonitis in 93.7%, fever in 92.5%, arthralgia in 47.4%, pleuritis in 31.2%, myalgia in 39.6% and erysipelas-like erythema in 20.9% of patients is seen. FMF is an autosomal recessive disorder found especially in Eastern Mediterranean countries. FMF is a recessive genetic disease associated with missense and nonsense mutations in MEFV gene, which is located on short arm of chromosome 16 (5). This gene codes for protein known as pyrin or marenostrin. Multiple mutations are located in MEFV gene. Most of mutations are in exon 10 of the gene between amino acids 680 and 761. One mutation in exon 1 at amino acid 148 may represent as many as 1 quarter of known mutation.

The MEFV gene consists of 10 exons and 781 codons and has so far shown over 50 mutations and polymorphisms (6). The most important long-term complication of FMF is secondary amyloidosis. Amyloidosis develops in patients who are not treated until they are 40 years old. Early amyloidosis is found in 6% of cases. In some cases, amyloidosis develops following febrile serosal attacks, while in some of them amyloidosis develops without attacks (7). In untreated cases of FMF, renal amyloidosis develops first and is followed by nephrotic syndrome. AA amyloidosis secondary to FMF is deposited in many tissues and organs. In renal involvement, proteinuira, nephrotic syndrome, uremia and end stage kidney failure can be found (8).

Renal transplantation with colchicine treatment is safe and successful in CKD stage-V secondary to AA amyloidosis due to FMF (9). In the KTrs, maintenance colchicine treatment prevents FMF symptoms and depo-sition of amyloidosis (10). Sherif et al have followed 23 kidney transplant patients with FMF-AA amyloidosis in the post-transplant period for 10 years. According to their paper, recurrence of amyloidosis developed in only one patient who stopped using colchicine, while recurrence was not observed in the patients treated with colchicine (11).

In all our cases, FMF was diagnosed during the post-transplant follow-up period. None of them had a family history of FMF. However, after the diagnosis of FMF only in one KTr was FMF also diagnosed in his nephew. All patients received a first transplantation. Among our patients, abdominal pain was the most frequent symptom for application to the hospital. Other reasons were fever, acute renal failure, arthralgia, malaise and nausea. In some cases, clinical presentation was similar to acute rejection. While the FMF mutation test was positive for three of the patients, one of them was negative, however, the abdominal pain attacks of this patient regressed prominently with colchicine treatment. The patients started to receive colchicine treatment as soon as they were diagnosed. Biopsy of the transplanted kidney was not performed for recurrence of amyloid deposition. Amyloid deposition of other tissues also did not show recurrence of amyloidosis of the transplanted kidney.

In summary, in 4 KTrs, FMF was diagnosed in the post-transplant period. Because attacks of this illness are seen intermittently and the disease is not frequent, FMF cannot be diagnosed until the post-transplant period, as in our patients. After renal transplantation, FMF attacks may often not be taken into account in situations of urgent treatment and hospitalization, such as fever, acute kidney failure, abdominal pain, rejection and infection. FMF diagnosis should always be kept in mind with abdominal pain attacks, since it has an unsolved etiology in Mediterranean countries and especially in our country. With correct diagnosis, unnecessary hospitalization and treatment and loss of organ functions including the transplanted kidney due to amyloidosis will be prevented, patient quality of life will be improved and other family members will be able to receive earlier diagnosis.

Conflict of interest

The authors declare no conflicts of interest.

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