CASE REPORT

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Familial Mediterranean fever-associated renal amyloidosis: case report and review of the literature

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Abstract

Familial Mediterranean fever (FMF) is a hereditary autoinflammatory disease, which is diagnosed especially in Mediterranean patients, but is a rare disorder in our geographical area. Due to its rarity and symptoms consisting mainly in recurrent episodes of fever and serositis, it may be mistaken with other, more frequent diseases, especially acute abdomen and systemic rheumatic diseases. The most important life-threatening complication is secondary amyloidosis, which usually affects kidneys, with proteinuria up to nephrotic syndrome and chronic kidney disease progressing to end-stage renal disease requiring dialysis or transplantation. In patients with suspected amyloidosis, kidney biopsy or submucosal rectal biopsy are the methods of choice for diagnosis. Kidney biopsy is also useful in patients with FMF who start to develop proteinuria, since other non-amyloid glomerular involvement may appear in FMF. Colchicine is now the gold standard for treatment, not only to reduce the frequency of attacks but also to improve renal prognosis. For this reason, the sooner the diagnosis is established the better the prognosis will be since the patient will benefit from the appropriate treatment with Colchicine. We present the case of a young female patient diagnosed through kidney biopsy with amyloid A (AA) amyloidosis after 30 years of evolution of FMF and we review the present knowledge regarding the pathogenesis and management of this rare genetic disease.

Keywords: familial Mediterranean fever, amyloidosis, Colchicine.

Introduction

Familial Mediterranean fever (FMF), also known as recurrent polyserositis, benign paroxysmal peritonitis, benign recurrent polyserositis, Wolff periodic disease, Reimann periodic disease, Siegal–Cattan–Mamou disease, or familial paroxysmal polyserositis, is a rare genetic disease mostly seen in patients of Mediterranean ancestry [1]. The disease is characterized by recurrent episodes with abrupt onset of fever, serositis (especially peritonitis) and arthritis (usually affecting large joints) and spontaneous resolution after few days. Disease is rarely seen in other populations and because of this, a high index of suspicion is needed for diagnosis, also because the disease is mimicking other more frequent diseases, especially autoimmune rheumatic ones. The most important complication of FMF is secondary amyloidosis due to sustained synthesis of serum amyloid A (AA). Compared to primary amyloidosis and other causes of secondary amyloidosis, in which amyloid deposition is usually systemic, in FMF kidney is the major organ involved by fibrillary deposits and renal amyloidosis is the main cause of morbidity and mortality in this disease [2]. Major consequences of renal amyloidosis in FMF are hypertension, glomerular proteinuria (with nephrotic syndrome in severe cases), progressive chronic kidney disease (CKD) up to end-stage renal disease (ESRD) and eventually death in the absence of renal replacement therapy [1]. It is essential to carefully follow-up any patient diagnosed with FMF for this renal complication, in order to promptly diagnose it and proper treat it. Colchicine is now the treatment of choice for this genetic disease and this drug also greatly improved patients' renal prognosis. Second-line options for treatment when Colchicine is ineffective or in case of side effects include anti-interleukin 6 (anti-IL-6) monoclonal antibodies (such as Rilonacept, Anakinra or Canakinumab) [3].

Aim

We present the case of a young female with FMF, with debut in early childhood and who developed mild proteinuria with no other signs of kidney disease (raised blood pressure or CKD), kidney biopsy revealing secondary amyloidosis.

Case presentation

The patient is a 36-year-old white female who was admitted in our Department of Nephrology to investigate the etiology of proteinuria, a urinary lab abnormality which was diagnosed two months before. The patient started to present at the age of 6 recurrent episodes (with weekly appearance) lasting for 48 to 72 hours of paroxysmal fever (up to 40ºC) accompanied by severe abdominal pain (located especially in the upper right abdominal quadrant), with flatulence and occasionally constipation, usually accompanied by myalgia and arthralgia, with inflammatory signs of the big joints (usually involving both knees). She was known since 6 years old with chronic inflammatory syndrome [raised erythrocytes sedimentation ratio (ESR) and C-reactive protein (CRP)], with augmentation during

attacks. Because of all these manifestations, juvenile rheumatoid arthritis was suspected and patient received during childhood a six months course of corticosteroid therapy, with moderate improvement of the disease (the free period between attacks was longer), but the symptoms appeared again with the same intensity and periodicity after the steroids were stopped. At 31 years old, she performed a magnetic resonance imaging of the lower spine, which showed mild sacroiliitis, which was considered to be reactive arthritis due to enteric infection with *Klebsiella*. One year after, endometriosis was suspected due to recurrent episodes of abdominal pain accompanied by presence of minimal ascites at the level of Douglas pouch, at abdominal ultrasound, and for this reason a laparotomy was performed, but during surgery, no changes were found inside peritoneal cavity. Four months before admittance in our Department, the diagnosis of FMF was suspected and for this reason a trial of Colchicine at a dosage of 1 mg/day was started; under this treatment, the attacks disappeared, but the symptoms reappeared again when patient decided to stop the treatment. Two months before admittance in our Department, she started to develop mild proteinuria (initially 350 mg/day) with progressive increase up to 500 mg/day and for this reason she was admitted in our Department. Her family medical history was without significance, she denied any known Mediterranean ancestry and she had a negative history of consanguinity.

At admittance, she was with good overall status, and the clinical exam was unremarkable, including normal blood pressure. Blood lab analyses were normal (including normal red and white blood cells number and normal creatinine 0.66 mg/dL), with the exception of inflammatory syndrome (serum fibrinogen 547 mg/dL, ESR 46 mm at one hour, CRP 17 mg/L). Urinalysis revealed proteinuria 650 mg/day, urinary sediment was normal (no red blood cells, no leukocytes, no casts). Abdominal ultrasound showed symmetric kidneys with normal dimensions and ultrasound appearance and presence of small ascites at the level of Douglas pouch. Blood analyses were performed in order to search for autoimmune disorders or viral infections with possible kidney involvement, including hepatitis B and C infection, human immunodeficiency virus, autoimmune rheumatic diseases [anti-streptolysin O antibody and complement C3 and C4 titers were normal, antinuclear, double-stranded deoxyribonucleic acid (dsDNA) and anti-Smith (anti-Sm) antibodies, cryoglobulins, rheumatoid factor, anti-neutrophil cytoplasmic, anti-glomerular basement membrane, anti-Ro and anti-La antibodies, antiphospholipid antibodies were all negative]. Thyroid hormones were normal. A detailed history of our patient did not found signs of possible nephrotoxic drugs.

Due to the patient's history of symptoms, we suspected FMF with possible secondary renal amyloidosis, explaining the presence of proteinuria. For these reasons, Colchicine at 1 mg/day dosage was started again. Nevertheless, because FMF may be associated also with other non-amyloid kidney disease, a kidney biopsy was performed in order to investigate the cause of proteinuria (Figure 1). It consisted of one core of renal cortex and medulla. Immunofluorescence was negative. Toluidine Blue staining was performed for light microscopy, because our Laboratory of Pathology uses Epon-embedded specimens (for Congo Red staining, paraffin embedding is needed). Fragment for light microscopy had seven glomeruli, two of them being globally sclerosed; the rest of five glomeruli had amorphous deposits inside the mesangial area. Same type of deposits was identified in the walls of the arterioles. Tubular atrophy with thyroid follicles-like appearance was also observed. Electron microscopy showed presence of non-branching and randomly arranged fine fibrils, typically for amyloid fibrils in the mesangium and occasionally thickening of glomerular basement membrane due to the presence of the same type of deposits (Figures 1 and 2). Foot processes of the podocytes were normal. The final histological diagnosis was renal amyloidosis. Treatment with Colchicine was well tolerated, without any gastrointestinal, liver or hematological side effects. At the check-up after three months, the patient was asymptomatic, without relapses of the attacks due to FMF and proteinuria dropped to 450 mg/day.

Discussions

This case is a good example of the importance of kidney biopsy in diagnosis and management of patients with suspected kidney involvement in a rare genetic disease especially for our geographic area, FMF.

FMF is a genetic disease mostly seen in patients with Mediterranean ancestry [1]. Most of the cases are due to nonsense or misense mutations of Mediterranean fever (*MEFV*) gene located on the short arm of chromosome 16 [2]. However, in 10–15% of all the patients fulfilling the criteria for diagnosis for FMF, no gene mutations are identified, so maybe other, yet not already identified genes, may be implicated, at least in these patients. For this reason, also genetic testing has a 70–80% positive predictive value [3]. The gene is coding pyrin, (or *marenostrin*, a term coming from "our sea" in Latin, due to Mediterranean origin of most of the patients), a protein expressed especially in neutrophils. Pyrin is involved in the control of the innate immunity especially by regulating the inflammasome assembling; in patients with altered pyrin structure or synthesis, neutrophils are secreting interleukin-1β (IL-1β) in excess, and this is the main reason which stays behind symptoms of the disease, characterized by recurrent episodes of fever accompanied by inflammation of the serous layers (peritoneum, pleura, pericardium and joints). Biological drugs acting against IL-1 are useful for treatment of this disorder. Until now, 218 mutations have been identified; among these, five mutations (*M694V*, *M694I*, *V726A*, *M680I*, and *E148Q*) are responsible for more than 75% of all cases, and homozygosity for *M694V* (seen especially in Sephardic Jews) is associated with the most severe forms of the disease [3, 4]. In almost all cases, the inheritance is recessive, although autosomal dominant and pseudo-dominance patterns were described in very few cases [5].

The exact pathogenesis of the disease is not completely understood. It may be due to dysregulated neutrophils, which become activated by otherwise mild proinflammatory stimuli thus releasing IL-1, with further recruitment of neutrophils and augmentation of the inflammation and finally the attack of the FMF. The first attack appears in 65% of patients before the age of 10 (at 6 years old in our patient) and in up to 90% of patients before the age of 20 [6].

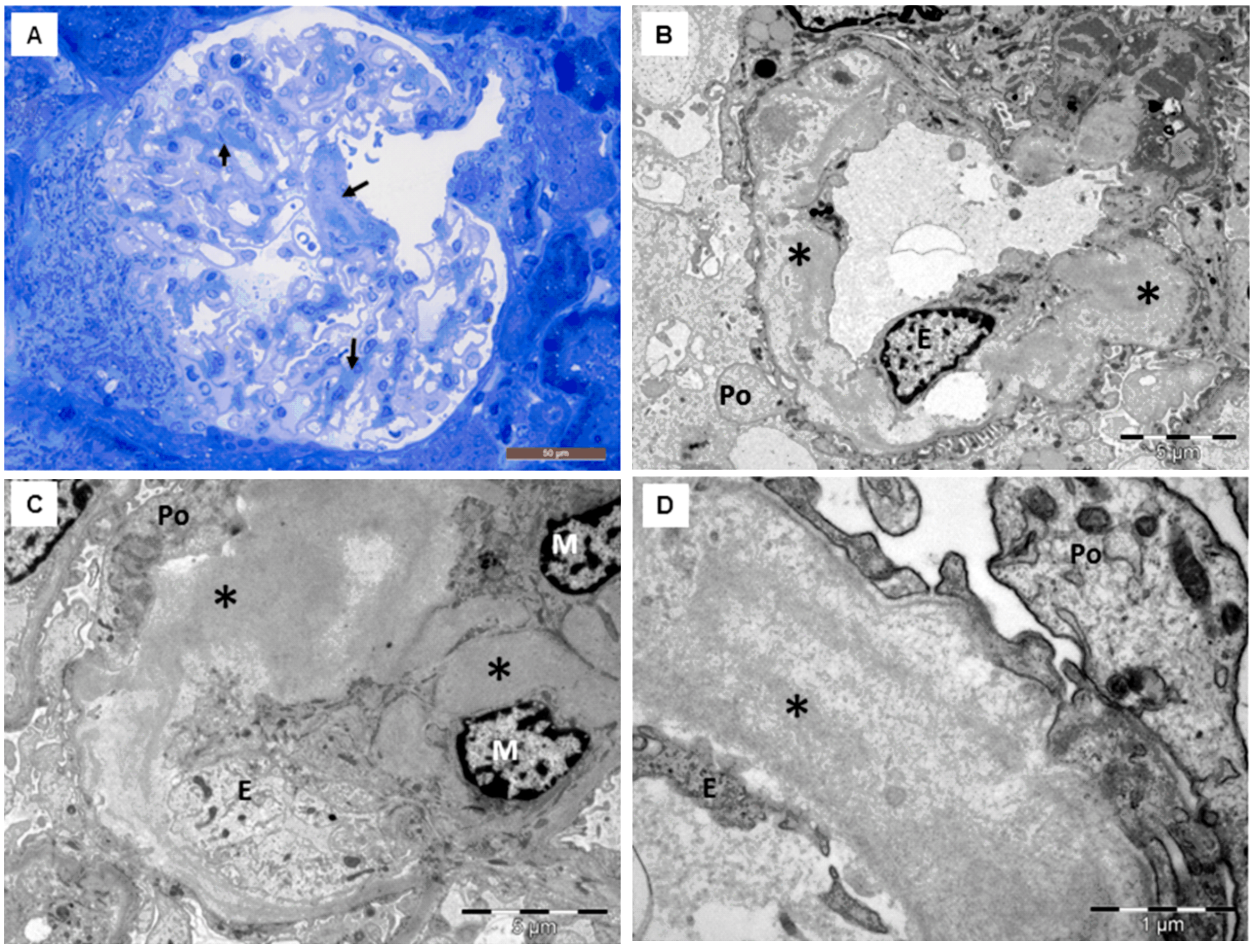

Figure 1 – ***Light microscopy (A) shows segmental enlargement of mesangial axis (arrows) (Toluidine Blue staining). Transmission electron microscopy (B–D) shows randomly deposits of fibrils with a diameter of 8–12 nm (*) located in glomerular basement membranes and mesangium. E: Endothelial cell; M: Mesangial cell; Po: Podocyte.***

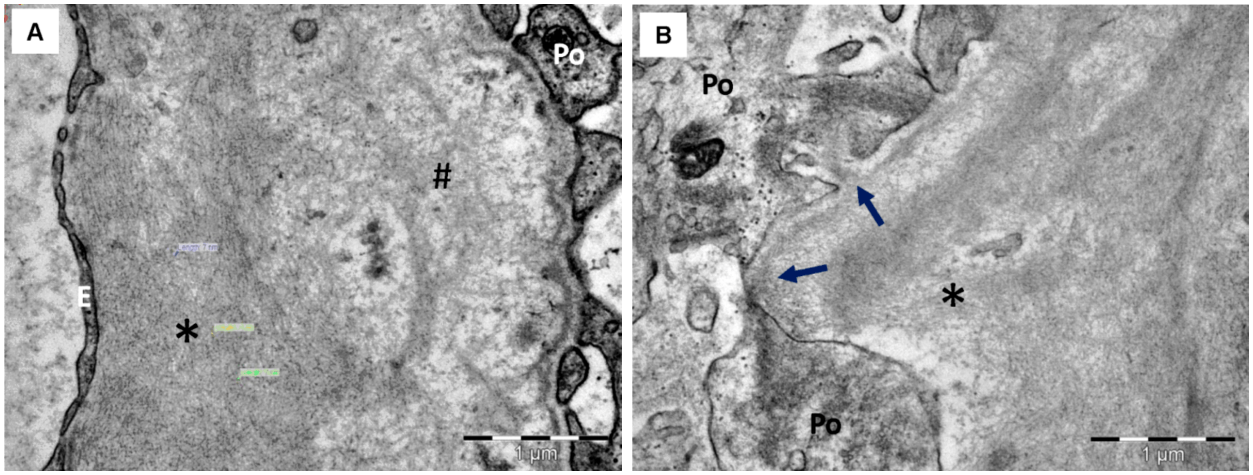

Figure 2 – ***Transmission electron microscopy shows typical amyloid fibrils: (A) About 7 nm diameter, non-branching and randomly arranged fibrils, densely (*) or loosely (#) packed into glomerular basement membranes thickness; (B) Amyloid (*) spicules (arrows) directly project into the podocyte (Po). E: Endothelium .***

Onset after age of 40 is extremely rare. The typical attack lasts for 48 to 72 hours, but the maximum intensity is during the first 12–24 hours. It consists of high fever usually accompanied by abdominal pain, either generalized or localized (like in our patient), sometimes mimicking acute abdomen, with constipation (or flatulence, like in our patient) usually followed by diarrhea (after the resolution of the attack), or replaced by diarrhea in children. Due to inflammation of the peritoneum, our patient associated small quantity of ascites, which was mistaken, due to associated abdominal pain, with pelvic inflammatory disease and endometriosis. Repeated episodes of peritoneal inflammation might generate adhesions complicated with small bowel obstruction. During crisis, patients often have inflammation of the big joints (hip, knees, elbows, ankles) and this symptom in some cases have a gradual resolution,

in up to 5–7 days. Some patients may associate seronegative spondyloarthropathy, and maybe this is the explanation why our patient was diagnosed at 31 years of age with reactive arthritis. Due to fever accompanied by serositis, misdiagnosis is quite often, especially in population with a low incidence of this disease, and this is the explanation for unnecessary laparotomies (as in our patient) and even appendectomies or cholecystectomies. Some patients may present with skin rash during crisis, especially with erysipelas-like appearance. During attacks, patients may develop also acute inflammation of the genitalia (either testis or ovaries) and if this complication appears repeatedly, patients may develop infertility during long-term [7]. Our patient never got pregnant. Myalgia may accompany attacks (like in our case), it involves lower limbs or it may be diffuse, sometimes it lasts for weeks, responds poor to Colchicine, may mimic fibromyalgia, it never associates increase in muscle enzymes and the underlying pathogenesis is not known, some suggesting that it is due to an accompanying vasculitic process [8]. During attacks, patients associate important inflammatory syndrome (leukocytosis with neutrophilia, raised serum fibrinogen, ESR and CRP), with gradual decrease thereafter, but patients with more severe forms remain with moderately inflammation between attacks, and these patients are at higher risk of developing amyloidosis, due to a sustained release of serum AA, an acute reactant protein. In-between attacks patients are completely asymptomatic [9].

FMF diagnosis is merely a clinical one. Criteria for diagnosis were developed by Tel HaShomer Hospital in Israel and are now worldwide accepted. The sensitivity of these criteria is estimated to be >95% and the specificity >97% [10]. The genetic testing is not routinely indicated, since its sensitivity is much lower, so a negative testing does not exclude diagnosis. Since the whole clinical picture of our patient was highly suggestive of FMF, including the positive response to Colchicine, because kidney biopsy also confirmed presence of amyloid, and also due to financial restraints, we initially did not perform genetic analysis. However, one year later we were able to perform this, demonstrating a double heterozygous mutant genotype *M680I*/*M694I* for FMF alleles.

Differential diagnosis includes other febrile hereditary diseases, arthritis with febrile onset, systemic rheumatic diseases, systemic vasculitis, infections, febrile malignancy and other causes of acute abdominal pain (Table 1).

The most important long-term FMF complication is secondary amyloidosis due to deposition of serum AA in the form of amyloid. Compared with other systemic amyloidosis, in FMF kidney is usually the only organ affected, although amyloid deposits may be identified in submucosal rectal specimens, but without clinical significance. In rare cases, involvement of other organs was described, such as thyroid, liver, spleen, testis, lung or heart [11]. Amyloid is a special form of protein deposition, giving at X-ray examination an aspect of diffraction in the form of anti-parallel β-sheets. Besides X-ray exam, amyloid may be identified using metachromatic staining (like Congo Red or Thioflavin-T) or by electron microscopy (randomly deposits of fibrils with a diameter of 8–12 nm, like we seen in our patient). The deposits are found mainly in the glomerulus (especially in the mesangial area and glomerular basement membrane, where they destroy the glomerular filtration barrier with development of glomerular proteinuria up to nephrotic syndrome), but it may also be identified in the walls of arterioles and small arteries and sometimes in the tubular basement membrane [12].

Table 1 – *FMF differential diagnosis*

Periodic febrile hereditary syndromes ▪ PFAPA; ▪ TRAPS (familial Hibernian fever) – conjunctivitis, periorbital edema, focal migratory myalgias, rash, abdominal pain, and occasionally monoarthritis H; ▪ HIDS – cervical lymphadenopathy, abdominal pain, vomiting or diarrhea, elevated levels of IgD; ▪ CAPS – urticarial rashes accompany episodic fevers.
Arthritis with febrile onset ▪ Systemic juvenile idiopathic arthritis (in children); ▪ Still's disease (in adults).
Systemic vasculitis with abdominal involvement ▪ Behçet's disease; ▪ Henoch–Schönlein purpura; ▪ Polyarteritis nodosa.
Systemic rheumatic diseases ▪ Systemic lupus erythematosus; ▪ Rheumatoid arthritis.
Infections ▪ *Borrelia*; ▪ Human parvovirus B19.
Febrile malignancy ▪ Leukemia; ▪ Myelodysplastic syndromes; ▪ Lymphoma.
Other ▪ Acute intermittent porphyria; ▪ Appendicitis; ▪ Cholecystitis; ▪ Pelvic inflammatory disease; ▪ Hereditary angioedema; ▪ Pancreatitis.

FMF: Familial Mediterranean fever; PFAPA: Periodic fever, aphthous stomatitis, pharyngitis, adenitis; TRAPS: Tumor necrosis factor (TNF) receptor-1 associated periodic syndrome; HIDS: Hyper-immunoglobulin D (IgD) syndrome; CAPS: Cryopyrin-associated periodic syndrome.

The most prominent symptom is proteinuria (with nephrotic syndrome in severe cases), usually without accompanying leukocyturia or hematuria. In the past, before the treatment with Colchicine was discovered, patients with severe FMF forms died before ages of 50 because of ESRD or complications due to nephrotic syndrome (especially pulmonary embolism because of renal vein thrombosis). Hypertension usually develops before onset of proteinuria, but in our patient blood pressure was normal. In severe cases, symptom-free periods are shorter, inflammatory syndrome persists between attacks and response to Colchicine may be incomplete or some patients are even refractory to this treatment. Once FMF diagnosis is established, it is extremely important to monitor the kidney function during the whole lifetime of the patient, especially by monitoring proteinuria. When proteinuria develops and becomes higher than 500 mg/day, kidney biopsy is always indicated in the absence of contraindications. Kidney biopsy is indicated not only to search for amyloidosis, but also because 40% of FMF patients may have FMF-associated non-amyloid kidney disease [especially focal segmental glomerulosclerosis, immunoglobulin A (IgA) and immunoglobulin M (IgM) proliferative mesangial nephropathy, membranous nephropathy, membranoproliferative glomerulonephritis and rapidly progressive glomerulonephritis] and some of these histological entities respond poor to Colchicine and need immunosuppressive agents [13, 14]. Main aims for FMF

treatment are prevention of attacks but most important prevention of amyloidosis. Although non-steroidal anti-inflammatory drugs or steroids may improve symptoms, they are not useful in preventing amyloidosis. One of the most important prognostic factors for renal amyloidosis is disease response to Colchicine and in the same time patient's compliance to treatment. Colchicine at a dosage of 1–1.5 mg/day is now the gold standard for treatment and is the drug which changed completely the prognosis of these patients, since it prevents the amyloid accumulation. At these doses, Colchicine inhibits neutrophils motility [15]. In patients with creatinine lower than 1.5 mg/dL, it may stabilize kidney function and ameliorates proteinuria [12]. Patients intolerant to or refractory to Colchicine may benefit from biological therapy, especially agents targeting either receptors for IL-1 (Anakinra and Rilonacept) or directly IL-1 (Canakinumab), but it is controversial whether these agents also reduce the risk for renal amyloidosis and for this reason Colchicine has to be continued if the patient is tolerating the drug [16]. In the present, ESRD develops only in patients that are non-compliant to Colchicine, cannot tolerate or are refractory to it and also to biological therapy. In the past, for ESRD patients, hemodialysis or kidney transplantation were the methods of choice as renal replacement therapies, as peritoneal dialysis was associated with increased risk of abdominal attacks due to FMF [12].

Although our patient seems to have a more severe form of the disease (with weekly attacks and with a permanent chronic systemic inflammation), kidney involvement appeared rather lately. Also, due to atypical manifestations of the disease, the diagnosis was established after 30 years from the debut; until then, the symptoms were confused with other, more frequent diseases, such as juvenile idiopathic arthritis and endometriosis. Immediately the proteinuria developed, we decided to perform a kidney biopsy, since we are aware that in this disease also non-amyloid glomerular involvement may appear and also to establish the prognosis of the kidney disease. Although patient had normal blood pressure and creatinine level at the moment when biopsy was performed, the result showed some chronic advanced lesions, with few glomeruli globally sclerosed and also with tubular atrophy. Nevertheless, since amyloid deposits are not so abundant, because Colchicine was well tolerated at least until now and since the symptoms respond to it we consider the patient has a good prognosis regarding renal amyloidosis.

Conclusions

Although FMF is a rare diagnosis for our geographical area, this diagnosis has to be taken into account in patients with symptoms suggestive for this disease, since a prompt diagnosis allows for a proper treatment with Colchicine, thus greatly improving not only patients' quality of life, but also renal prognosis. Kidney biopsy is useful in this instance not only to demonstrate presence of amyloid deposits, but also to diagnose other possible non-amyloid glomerular involvement which may benefit from other therapies, such as immunosuppressive agents.

Conflict of interests

The authors declare that they have no conflict of interests.

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