Fever of unknown origin in a haemodialysis patient: a late diagnosis requiring a novel treatment

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Introduction

Fever in haemodialysis patients is usually attributed to infection, with less frequent causes including malignancy and autoimmune disorders [1]. Sometimes, fever persists despite empirical treatment, and investigations towards the above mentioned diagnoses fail to reveal the cause. Thus, rarer etiologies need to be considered, which may appear rather unexpected, especially in patients under prolonged medical follow-up.

The case

A 54-year-old Greek male chronic haemodialysis patient presented with a 5-month history of recurrent episodes of fever. At presentation, he had a temperature of 38.4°C and a pulse rate of 105/min, arterial blood pressure was within normal limits and pulse oximetry showed oxygen saturation of 98% while breathing ambient air. Clinical examination was remarkable for decreased breath sounds over the right lung basis, a palpable, mildly enlarged, non-tender spleen, and a left forearm arteriovenous fistula for dialysis access without any signs of infection.

During the past 5 months, the patient had developed recurrent episodes of fever reaching 38.5°C, lasting up to 4 days. They occurred twice or thrice a month, without distinctive periodicity or association with the dialysis sessions, and were accompanied by malaise, chills, night sweats, and non-productive cough, without rigours, nausea, vomiting, diarrhoea, dysuria, rash, enanthema, arthritis, abdominal pain, back-pain, myalgia, uveitis or weight loss. The fever seemed to temporarily respond to oral paracetamol and broad spectrum antibiotics.

Imaging, including computed tomography of the neck, chest and abdomen, as well as trans-esophageal echocardiography, was remarkable for a right pleural effusion, a small pericardial effusion and mild splenomegaly, without evidence of liver pathology or portal hypertension. Subsequent pleural aspiration revealed a non-malignant, culture negative, transudate. Blood, urine and sputum cultures were negative as was serology for active infection by hepatitis B and C, Epstein Barr virus, cytomegalovirus and human immunodeficiency virus. A tuberculin sensitivity test was negative, as well as serology for toxoplasma, brucella, and legionella. Autoantibody serology, including anti-neutrophil cytoplasmic antibodies, anti-nuclear antibodies, antibodies to extractable nuclear antigens, anti-dsDNA antibodies, was also negative, except for a low anti-smooth muscle antibody titre (1:40).

The patient also displayed anaemia requiring blood transfusions, resistant to maximal erythropoietin administration and iron supplementation, with a ferritin of 820 ng/mL and transferrin saturation of 45%. Upper and lower gastrointestinal endoscopy revealed no haemorrhagic foci. Bone marrow aspiration and trephine revealed no evidence of myeloproliferative disorder. Serum protein electrophoresis was negative for the presence of monoclonal immunoglobulins. His parathormone was well controlled (intact parathormone: 260 pg/mL, reference range 15–65 pg/mL) with intravenous paricalcitol (2,5 mg/thrice weekly). His white blood cell count ranged from 6010 to 11600/μL and his C-reactive protein from 12 to 90 mg/L (reference range <8 mg/L) peaking during fever attacks. He was dialysed three times weekly for 4 h with a synthetic low flux dialyser, enoxaparin anticoagulation and bicarbonate dialysate, to a weekly Kt/V of 1.8.

The patient had started renal replacement therapy 5 months previously, after a 10-year history of proteinuric nephropathy, which had presented with a nephrotic syndrome. An initial renal biopsy was consistent with minimal change disease, which, however, proved to be steroid resistant. A second renal biopsy after 5 years, with non-nephrotic proteinuria and rising creatinine, was consistent with focal and segmental glomerulosclerosis (FSGS).

He was an active high school teacher, and admitted to smoking and social ethanol consumption, denying any illicit drug use. He lived alone with his pet cat. He had not travelled abroad recently and denied any recent history of recurrent fevers prior to the initiation of dialysis. He reported having fevers in childhood with few episodes of febrile seizures as a baby. Splenomegaly was diagnosed after hepatitis A infection in his teens. He had undergone

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thyroidectomy at the age of 38, because of a goitre, and was on oral thyroxine, with normal thyroid stimulating hormone levels. He had no family history of fevers or kidney disease. During the last admission, after yet another interrogative history taking, he recollected having an episode of ‘gout’ about 20 years before, which had responded to oral colchicine.

Due to the lack of evidence supporting an infectious, malignant or autoimmune cause for his febrile illness, and because of the history of arthritis and presence of the pleural and pericardial effusions, the diagnosis of a periodic fever syndrome was considered. He was initiated on oral colchicine, 0.5 mg tid, for familial Mediterranean fever (FMF). The treatment was effective and well tolerated, with remission of fevers. Haemoglobin levels rose gradually with lowering doses of colchicine. The treatment was effective and well tolerated, with remission of fevers. Haemoglobin levels rose gradually without the need for transfusions, with lowering doses of colchicine.

However, 17 months after the initiation of colchicine treatment periodic fevers with similar accompanying symptoms and erythropoietin-resistant anaemia recurred. After excluding any infectious causes, the dose of colchicine was increased, but was not well tolerated, due to the development of diarrhoea, despite a lactose-free diet. The patient consented to the off-label administration of the interleukin 1 receptor antagonist (IL-1Ra) anakinra, 100 mg sc, at the onset of prodromal symptoms (malaise, chills), which seemed to occur every 48–72 h, while continuing oral colchicine at 0.5 mg tid. Because of only partial response the patient was switched to 100 mg sc, at the onset of prodromal symptoms (malaise, chills), which seemed to occur every 48–72 h, while continuing oral colchicine at 0.5 mg tid. Because of only partial response the patient was switched to 100 mg sc, at the onset of prodromal symptoms (malaise, chills), which seemed to occur every 48–72 h, while continuing oral colchicine at 0.5 mg tid. Because of only partial response the patient was switched to 100 mg sc, at the onset of prodromal symptoms (malaise, chills), which seemed to occur every 48–72 h, while continuing oral colchicine at 0.5 mg tid. Because of only partial response the patient was switched to 100 mg sc, at the onset of prodromal symptoms (malaise, chills), which seemed to occur every 48–72 h, while continuing oral colchicine at 0.5 mg tid. Because of only partial response the patient was switched to 100 mg sc, at the onset of prodromal symptoms (malaise, chills), which seemed to occur every 48–72 h, while continuing oral colchicine at 0.5 mg tid. Because of only partial response the patient was switched to 100 mg sc, at the onset of prodromal symptoms (malaise, chills), which seemed to occur every 48–72 h, while continuing oral colchicine at 0.5 mg tid. Because of only partial response the patient was switched to 100 mg sc, at the onset of prodromal symptoms (malaise, chills), which seemed to occur every 48–72 h, while continuing oral colchicine at 0.5 mg tid. Because of only partial response the patient was switched to 100 mg sc, at the onset of prodromal symptoms (malaise, chills), which seemed to occur every 48–72 h, while continuing oral colchicine at 0.5 mg tid. Because of only partial response the patient was switched to 100 mg sc, at the onset of prodromal symptoms (malaise, chills), which seemed to occur every 48–72 h, while continuing oral colchicine at 0.5 mg tid. Because of only partial response the patient was switched to 100 mg sc, at the onset of prodromal symptoms (malaise, chills), which seemed to occur every 48–72 h, while continuing oral colchicine at 0.5 mg tid. Because of only partial response the patient was switched to 100 mg sc, at the onset of prodromal symptoms (malaise, chills), which seemed to occur every 48–72 h, while continuing oral colchicine at 0.5 mg tid. Because of only partial response the patient was switched to 100 mg sc, at the onset of prodromal symptoms (malaise, chills), which seemed to occur every 48–72 h, while continuing oral colchicine at 0.5 mg tid.

Discussion

We present a rather extraordinary case of a haemodialysis patient, without evidence of renal amyloidosis, with a late diagnosis of FMF. Exacerbation of symptoms coincided with the initiation of dialysis and led to erythropoietin resistance, requiring blood transfusions. Favourable initial response to colchicine was followed by resistance to treatment, which was restored with IL-1R inhibition.

FMF is the most common inherited periodic fever syndrome [3]. It is an autosomal recessive disorder characterized by recurrent, self-limiting episodes of fever, accompanied by serositis and marked increase of acute phase reactants, including serum amyloid A (SAA), which may lead to the development of amyloidosis [4]. The diagnosis of FMF is mainly based on the Tel Hashomer clinical criteria [3]. Although mainly affecting populations around the Mediterranean basin, FMF may now be encountered worldwide due to intercontinental travel [3, 5]. The disease has been associated with mutations of the MEFV gene in chromosomes 16p [3, 5]. MEFV encodes a protein called pyrin or marenostrin, which is expressed mainly in neutrophils, where it appears to act as a regulator of the inflammatory response [3]. It is suggested that mutated pyrin results in uncontrolled inflammatory reaction [5]. Many different, predominantly single missense mutations have been described, which may be associated with variability in clinical expression and complications [5]. In the majority of cases FMF manifests before 20 years of age, although late presentations have been reported, interestingly also involving R202Q/R202Q homozygosity, as in our case [6]. Furthermore, association of R202Q/R202Q homozygosity with atypical FMF presentation has been reported in a FMF cohort from Greece [2].

The most common renal manifestation of the disease is the development of SAA amyloidosis, presenting clinically as nephrotic syndrome, and eventually leading to end-stage renal failure [3, 7]. The prevalence of renal amyloidosis appears to be independent of the frequency and severity of flares, and has been reduced after the widespread use of colchicine treatment [3]. Ethnic and geographic variability in the development of renal amyloidosis has been described, and is probably the result of genetic and environmental influences [3, 7]. Non-amyloid renal involvement has also been described, although a casual association with FMF cannot be verified [3]. It includes IgA nephropathy, IgM nephropathy, membranoproliferative glomerulonephritis and rapidly progressive crescentic glomerulonephritis [8, 9], one case of the latter responding to pulse methylprednisolone and cyclophosphamide treatment [9]. Both renal biopsies of our patient did not show any amyloid or immune deposits, and to the best of our knowledge it is the first case of FSGS described in a patient with FMF.
In our patient, initiation of dialysis was associated with exacerbation of symptoms, and with epoetin-resistant anaemia, and this may be causal. In haemodialysis patients, peripheral blood monocytes produce and release pro-inflammatory cytokines, such as IL-1, IL-6 and TNFα, inducing the production of acute phase reactants, such as CRP and SAA, in response to direct contact of blood with the dialytic membrane, complement activation in the extracorporeal circulation, and backfiltration of bacterial material from the dialysate to the blood [10]. Impairment of inflammatory control mechanisms, as in the case of untreated FMF, may lead to a disproportionate inflammatory reaction. Furthermore, inflammation has been associated with anaemia due to iron sequestration in unknown reasons [11] and epoetin resistance in chronic haemodialysis patients [12].

Colchicine is the standard treatment of FMF [4, 13]. Response to colchicine represents a major clinical diagnostic criterion, with over 90% of patients experiencing amelioration of symptoms, while on treatment [4]. Colchicine reduces the inflammatory response by interfering with the formation of tubulin in neutrophils and by preventing neutrophil activation, chemotaxis and degranulation [13]. The most frequent complication is diarrhoea, which may be overcome by a lactose free diet [13]. Less frequent side effects include pancytopenia, myopathy and rash [3]. For unknown reasons ~5–10% of patients do not respond to colchicine [14], the only difference identified so far being a lower level of colchicine in the monocytes of the non-responders [15]. Our patient responded initially, with remission of fever episodes and restoration of erythropoiesis, before developing resistance to colchicine after 1 year of treatment.

To the present date no consensus exists regarding alternative treatments for colchicine-resistant FMF. Several immunomodulating treatments have been used, including interferon-α, thalidomide and anti-TNFα agents [16]. The established role of IL-1 in the induction of the inflammatory response, initially augmented by pyrin mutations, led to the evaluation of IL-1 antagonism in the treatment of FMF, with encouraging results from a small number of cases [17], and a small randomized trial [18]. In dialysis patients IL-1 receptor antagonism seems an appealing option, since it has been shown to reduce haemodialysis-associated inflammation [19]. Anakinra is an analogue of the natural IL-1 receptor antagonist. It inhibits binding of IL-1α and IL-1β to the IL-1 receptor [17], and has previously been reported as an effective and safe alternative to colchicine in individual cases of FMF patients on dialysis [20]. The current experience of anakinra pharmacokinetics in renal failure is limited, although a dose of 100 mg × 3/week seems effective and safe [20]. However, caution regarding serious side effects, such as neutropenia, is strongly advised [20]. After 12 months of treatment, our patient remains symptom free, without the need for blood transfusions and without any complications associated with IL-1Ra treatment.

**Teaching points**

(i) Periodic fever syndromes should be considered in the differential diagnosis of fever of unknown origin in all patients of all ages, as certain forms may manifest late in life.

(ii) FMF may be associated with non-amyloid-related nephropathy leading to end-stage renal disease, although there is currently no proof of causality.

(iii) Haemodialysis is a pro-inflammatory process, which may lead to acute clinical presentations in patients with a predisposition to dysregulated inflammatory response.

(iv) In haemodialysis patients, non-septic inflammation may cause epoetin resistance requiring blood transfusions.

Conflict of interest statement. None declared.

**References**


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