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Teaching Point
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Periodic fever syndrome with relapsing glomerulonephritis: a case report and teaching points

Mykola V. Tsapenko[1], Timothy G. Call[2], John A. Lust[2] and Nelson Leung[1,2]

[1]Division of Nephrology and Hypertension, Department of Internal Medicine, Mayo Clinic, Rochester, MN, USA and [2]Division of Hematology, Department of Internal Medicine, Mayo Clinic, Rochester, MN, USA

Correspondence and offprint requests to: Mykola V. Tsapenko; E-mail: mykolatsapenko@yahoo.com

Abstract
We report a case of relapsing mesangial and endocapillary proliferative glomerulonephritis (GN) associated with a periodic fever syndrome. The patient presented 11 times in >4 years with acute febrile episode followed in 1–3 days by hematuria, thrombocytopenia and other symptoms of acute GN with variable severity of acute kidney injury. In three episodes, the patient required renal replacement therapy for 7, 10 and 2 treatments, respectively. Shortly after the acute symptoms of the febrile episode had resolved each time, the kidney function would recover and the serum creatinine would return to baseline. Two kidney biopsies obtained during separate episodes showed acute tubular injury along with morphological changes resembling post-infectious GN but with no clinical evidence to support an infectious etiology. Multiple treatment regimens were unable to control the disease. Symptoms were alleviated by rituximab but did not completely remit. Stable remission of the periodic fever and GN was finally achieved after anakinra therapy was initiated 18 months ago. Since then, the patient had several episodes of documented infection without high fever and nephritic kidney manifestations. His kidney function remained stable with normal serum creatinine.

Keywords: autoinflammatory reactions; glomerulonephritis; periodic fever

Introduction

Acute post-infectious glomerulonephritis (GN) is a glomerular immune complex disease induced by infective agents/antigens and usually presents as an acute nephritic syndrome within 1–3 weeks after onset of the infection. No standard therapy currently exists. In most of the cases, the disease has a very good prognosis. Recurrent biopsy-proven acute post-infectious GN is an extremely rare condition. Most of the cases are described in children with acute streptococcal infections [1]. It is even more uncommon in adults [2, 3]. We report a case of the recurrent mesangial and endocapillary proliferative GN with histological features resembling post-infectious GN in a patient with frequent recurrent febrile illness without evidence of infection who improved after treatment with rituximab and long-term anakinra therapy.

Case report

Presentation

A 58-year-old gentleman with a history of poorly controlled hypertension and monoclonal gammopathy of undetermined significance (MGUS) was admitted to our hospital with right lower extremity cellulitis complicated by the hematuria, thrombocytopenia and acute kidney injury (AKI). He initially came to our institution for a consultation on his MGUS and what was described as a recurrent post-infectious GN. Two days after arrival, the patient developed cellulitis and was started on oral cephalexin within 24-h of the initial symptoms. On the next day, he felt no improvement. He began to notice amber-colored urine exactly as it happened in three previous episodes that resulted in acute renal failure and he was later diagnosed as having recurrent post-infectious GN. This was his fourth episode (E4) of the recurrent GN, which prompted his admission to the hospital.

History of previous episodes of the recurrent GN

The patient suspected that his initial episode could have happened 8 years earlier after he went on a hunting trip and developed a viral syndrome. Within several weeks, he gained around 30 pounds and developed significant swelling associated with decreased urine output. He did not notice any hematuria. He was treated with steroids and furosemide, and the episode resolved. Nothing happened until 6 years later when he had his first (E1) of his many similar episodes. He developed a sore throat with high fever that was followed by gross hematuria, acute renal failure and profound thrombocytopenia (9×10^9/L) in 1–3 days. A renal biopsy was performed which showed

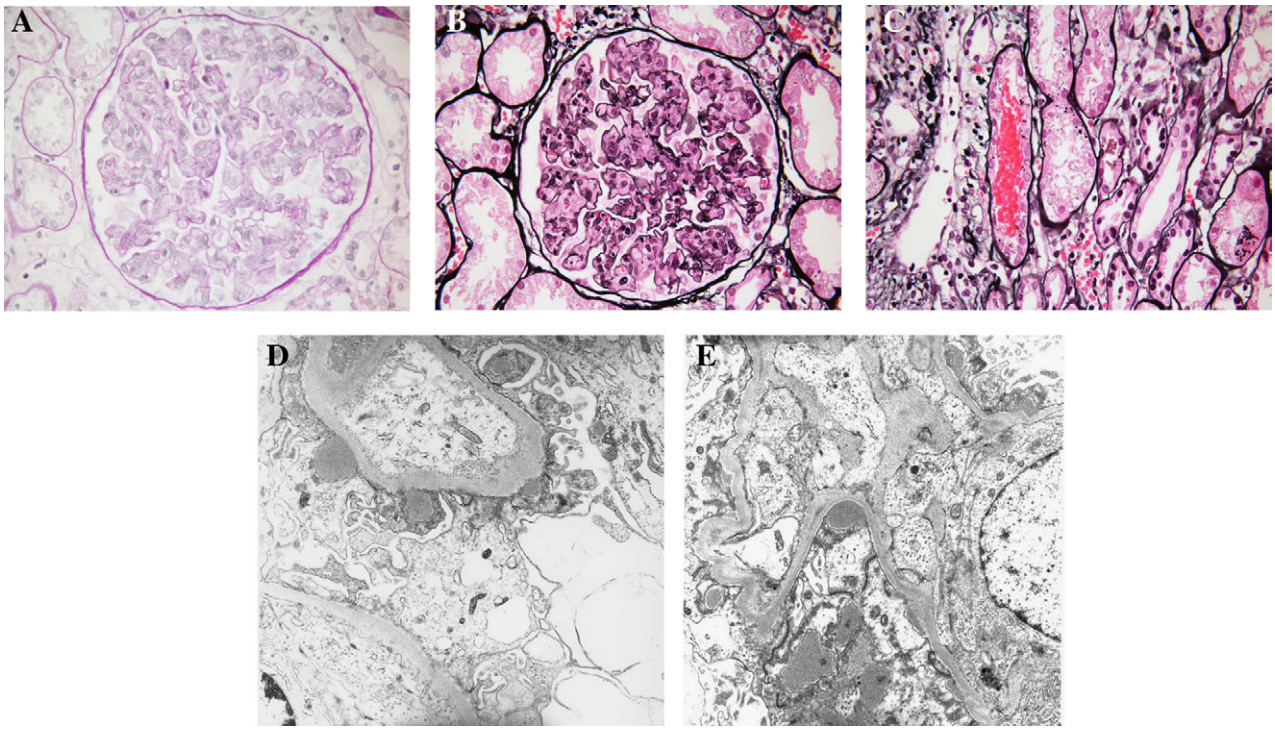

Fig. 1. Kidney biopsy during Episode 1 (E1): (**a**) periodic acid-Schiff stain, ×400; (**b**, **c**) Silver methenamine stain, ×400; (**d**, **e**) electron microscopy. The glomeruli show both mesangial and endocapillary proliferation with focally increased numbers of glomerular neutrophils. There is increased interstitial edema accompanied by a mild mixed inflammatory cell infiltrate. Focal mild fibrosis is also present. The tubules show epithelial cell attenuation and occasional tubules contain intra-luminal red blood cell casts. Large sub-endothelial hump-like deposits were ultrastructurally seen on EM along with 70–80% epithelial cell foot process effacement with microvillous transformation and cytoplasmic vacuolization. Immunofluorescent histology showed a very faint focal mesangial and capillary wall staining for IgG and a speckled mesangial and capillary wall staining for C3 (1–2+). There was a minimal mesangial staining for kappa light chain. Stains for IgA, IgM, C1q and lambda were negative (not shown). Morphological diagnoses: (i) acute post-infectious GN. (ii) Acute tubular injury.

changes consistent with post-infectious GN and acute tubular necrosis (Figure 1a–e). He was treated with steroids, antibiotics and required seven hemodialysis (HD) treatments before his kidney function recovered. His serum creatinine normalized. Next, a second episode (E2) occurred almost 24 months later with a very similar presentation: sore throat and high fever followed in 1–3 days by gross hematuria, acute renal failure and profound thrombocytopenia (10×10^9/L). He underwent a kidney biopsy which again found features of post-infectious GN and acute tubular necrosis (Figure 2a–d). This time he was treated with antibiotics, but no steroids. He required 10 HD treatments and ultimately completely recovered his kidney function. His third episode (E3) started 8 months later with exactly the same presentation and course. He was treated with antibiotics, but no steroids and required two HD treatments. The lowest platelets count was 19×10^9/L. Nine days after, the last HD patient presented to our institution for a second opinion. His kidney function was recovering but he still had an elevated serum creatinine at 2.6 mg/dL (230 mcmol/L). His platelet count, other hematologic parameters and complement levels were normal. It was interesting to note that blood cultures and other extensive infectious disease studies were negative for identifiable infections in all of the previously described episodes. Complement (both C3 and C4) level was low in each case with otherwise negative serum serological studies.

Hospital course of the fourth episode (E4) of the GN

On presentation, the patient had a platelet count of 468×10^8/mL and a creatinine of 2.6 mg/dL (230 mcmol/L) (Figure 3). A week later, while in the hospital, his platelet count had dropped to 40×10^9/L, and his creatinine was up to 3.2 mg/dL (283 mcmol/L). Eventually, his creatinine reached 6.1 mg/dL (539 mcmol/L) and he developed nephrotic-range proteinuria with a urine protein/osmolarity ratio of 7.46 [(mg × kg H_2O)/(mOsm × L)]. He was treated with high-dose intravenous (IV) steroids, which lead to resolution of the hematuria and improvement of the renal function and proteinuria. At admission, the patient's antibiotic regimen was switched to vancomycin which improved the cellulitis symptoms. He was dismissed with the creatinine of 4.6 mg/dL (407 mcmol/L) and by Day 10 of the episode, his creatinine was down to 2.2 mg/dL (194 mcmol/L). The platelet count at that time was 620×10^9/L.

Evaluation and workup of the GN during E4

Extensive workup for possible infections turned out negative: blood cultures × 2, urine culture, rickettsial panel, human immunodeficiency virus, hepatitis panel, Babesia, Antistreptolysin O titer (ASO), Ehrlichia, *Escherichia coli*, Lyme screen. Dengue fever titers were normal. Malaria smear was negative. Serum serology including anti-nuclear antibodies panel, antineutrophil cytoplasmic antibodies,

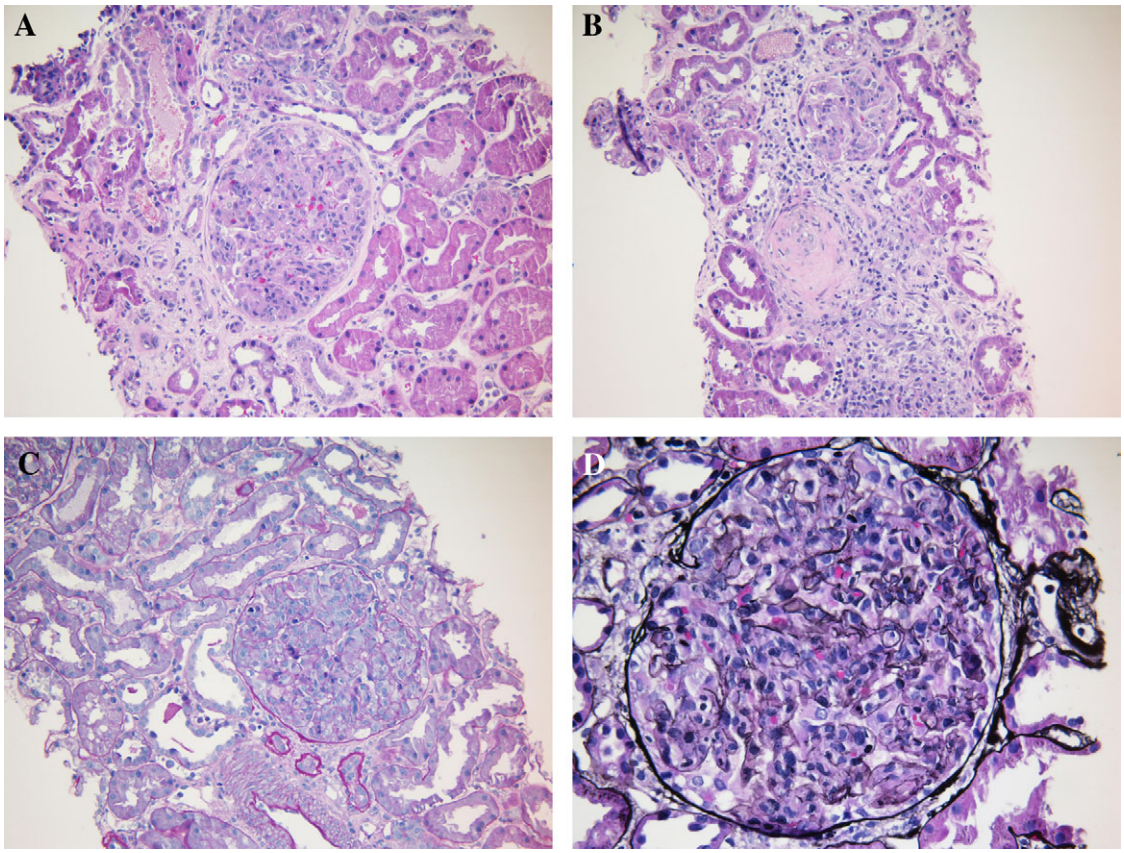

Fig. 2. Kidney biopsy during Episode 2 (E2). (**a**, **b**) Hematoxylin and eosin stain, ×100; (**c**) periodic acid-Schiff stain, ×200. (**d**) Silver methenamine stain, ×400. The glomeruli show both mesangial and endocapillary proliferation. A few glomeruli appear ischemic with capillary wrinkling and moderate periglomerular fibrosis. There is patchy interstitial fibrosis accompanied by collections of interstitial inflammatory cells, a few atrophic tubules and focal tubule dropout. Focal fibrosis is also present. Immunofluorescent staining showed an irregular, speckled capillary wall and mesangial staining for IgG (trace), C3 (1+) and C1q (trace). There was a faint cast staining for IgA (trace). Stains for IgM, kappa and lambda all were negative (not shown). Electron microscopy revealed hump-shaped sub-epithelial deposits with near-complete visceral epithelial cell foot process effacement (not shown). Morphological diagnoses: (i) acute post-infectious GN with focal global glomerulosclerosis, glomerular ischemic change and interstitial fibrosis. (ii) Acute tubular injury. (iii) Arteriosclerosis, minimal to mild.

anti-myeloperoxidase, anti-glomerular basement membrane (GBM), anti strep-O, anti-DNAse, kappa and lambda free light chains, cryoglobulin (at body temperature), proteinase 3, cyclic citrullinated peptide Ab were all negative. Serum protein electrophoresis shows a very small M-spike of 2 g/L in the gamma region. Immunofixation shows a monoclonal IgG kappa. Immunological workup revealed a low IgA (0.26 g/L), IgM (0.38 g/L), IgG (3.46 g/L), IgD (<0.01 g/L) as well as low total complement, C3 (0.32 g/L) and C4 (<0.06 g/L). Hematological workup was negative for thrombotic thrombocytopenic purpura (TTP): ADAMTS13 assay, anti-platelet Ab, coagulation study panel and serum lactate dehydrogenase level were all normal. No schistocytes or other features of hemolysis were appreciated on the peripheral smear. A bone marrow aspirate and biopsy revealed slightly hypercellular bone marrow (60% cellularity) with moderate megakaryocytic hyperplasia. No morphologic features of infection or lymphoma were identified. However, there were markedly increased iron stores.

Course after discharge from the hospital and subsequent episodes of the GN

At dismissal, he was placed on penicillin prophylactically although this was not effective at preventing these episodes from recurring. Two weeks after discharge and 3 days after completion of the steroid taper, the patient developed another (fifth, E5) episode of the GN with very same presentation. Again, he was started on high-dose IV steroids with quick taper leading to resolution of the hematuria and improvement of the AKI and thrombocytopenia. Hypocomplementemia improved in between the episodes. Two weeks later, on the last day of the steroid taper, the patient suffered another (sixth, E6) bout of the GN. This was again alleviated by high-dose steroids with a slow taper. Four weeks later, while on prednisone at 17.5 mg daily, the patient developed another (seventh, E7) episode of hematuria with elevated creatinine and profound thrombocytopenia. Interestingly, the patient recalled that these episodes were usually preceded by nasal stuffiness. Also, he would get a sore throat and sometimes lymphadenopathy in the cervical chains. He had been cultured many times and no organism had ever been identified. He recalled having periodic fevers when he was a child. These episodes usually occurred in the summer time and the fever would come 'out of the blue'. He would get over them without any lingering effects. The patient has two brothers with ataxia, and one may have had periodic fevers as well. His brothers were, however, diagnosed with Friedreich's ataxia. He is of

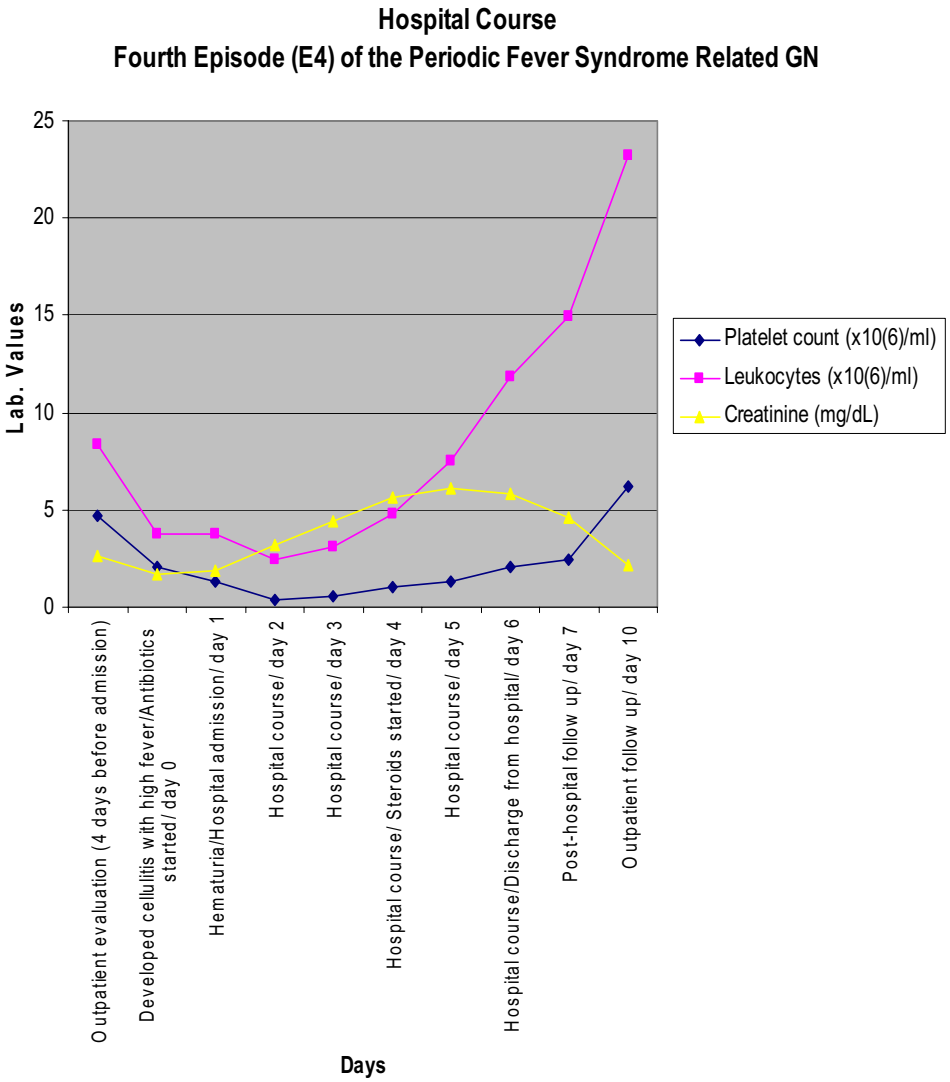

Fig. 3. Hospital course during PFS-related GN, Episode 4 (E4).

French and Spanish descent. After the E7 within 4 months, the patient had two more episodes (E8 and E9) while on steroids.

Treatment and resolution

After E9, we decided to treat him with rituximab (four doses of 375 mg/m^2). Incidentally, the patient developed pancytopenia after his rituximab infusion. He was treated with growth factors and blood counts recovered. Within a month of completing rituximab, he had two more episodes (E10 and E11) of GN with characteristic symptoms: urinary tract infection symptoms with high fever, followed in 1–3 days by hematuria, AKI and thrombocytopenia. These two episodes were the only two where his creatinine stayed <2 mg/dL and both episodes lasted <5 days. These were shorter than usual and suggested less severe manifestation of the disease. Both episodes occurred while he was on steroids and the dose was increased and slowly tapered. He had had a total of 11 episodes within the preceding 17 months. At which point, he was started on anakinra (100 mg subcutaneously every other day). With anakinra, he was able to completely taper off steroids. Since then, he had had several episodes of infections, but no more GN symptoms. We followed him for another 18 months and he appears to be disease free. There have been no adverse reactions to anakinra. The patient initially lost 25 pounds. Most of this was due to water weight, which was associated with an improvement of the peripheral edema. The weight loss eventually stabilized, and he has not lost any more weight for the last few months. The patient denies any fever. His kidney function had been stable with a normal serum creatinine, no proteinuria and normal urinary sediment. His energy level remained good and he returned to work full time.

Discussion

The present case has many interesting and unusual clinical features, which together do not fit any previously reported disease entity. It was an adult-onset recurrent GN with early

presentation (1–3 days) after relapsing fever episodes in the absence of associated viral or bacterial infection. Although the morphological features resembled post-infectious GN, the clinical picture was inconsistent with this disease entity, which included an early-onset acute GN, AKI, thrombocytopenia (without hemolysis), hypocomplementemia (both C3 and C4) and nephrotic range proteinuria followed by complete resolution of the symptoms and kidney function recovery. The patient had a total of 11 episodes within 17 months. Steroids had limited efficacy and antibiotics had no role in prophylaxis. Symptoms were alleviated but not prevented with rituximab (B-cell-depleting agent) therapy. Stable remission of the periodic fever and GN was achieved after anakinra [interleukin-1 type I receptor (IL-1RI) blocker] therapy.

The patient had two kidney biopsies performed during two different episodes (E2 and E3). In both cases, the light microscopy, immunofluorescent and electron microscopy findings were consistent with post-infectious GN (Figures 1 and 2). It was very puzzling with frequent recurrence of the symptoms and absence of the associated infection.

If we analyze mechanisms responsible for morphological features in our case, we should consider nephritis-associated plasmin receptor, one of the nephritic antigens for acute post-streptococcal GN. It can adhere to GBM and mesangium and subsequently bind plasmin and increase GBM permeability, which would result in immune complex deposition [4]. This antigen was considered to be responsible for the unusual morphological features of acute GN in patients with streptococcal infection presented as dense-deposit disease [5, 6] or Henoch–Schönlein purpura nephritis [7]. Lack of immune response to this antigen in children may be responsible for some atypical features of post-infectious GN and its recurrence [1]. There is even one report of post-infectious GN associated with hemolytic–uremic syndrome (HUS) [8]. However, in all reported cases, renal manifestations developed >2 weeks after the symptoms of infection, which was consistent with post-infectious GN but was not the case in our patient. We also did not find any evidence of HUS, TTP or other sign of hemolysis that would give a reasonable explanation for the transient, rapidly reversible profound thrombocytopenia.

Hypogammaglobulinemia and the low complement level (both C3 and C4) during the episodes suggested an immunological response with activation of the complement cascade as a part of the mechanism in the disease development. However, they could not explain an early onset of the GN and the recurrence of the disease and would rather suggest a non-specific inflammatory response. Although IgA deficiency was reported as a predisposing factor for recurrent post-infectious GN [2] or membranous nephropathy [9], mainly via the inability to control repetitive infections, we do not believe this could explain recurrence of the GN in our case since no infectious agent was ever identified. We would instead speculate that the main triggering mechanism for the disease was related to autoinflammatory reactions characterized by high fever and other signs of inflammation without actual infection in any of the 11 episodes. Successful therapy with anakinra supports this idea. There is a group of genetically determined diseases that fit into this description: periodic fever syndromes (PFS). They all share the common feature of a cytokine-mediated autoinflammation associated with a self-limiting febrile attack in the absence of antigen-directed autoimmunity. Recent studies have shown that activation of the interleukin-1beta pathway is a common mechanism in the pathogenesis of the autoinflammatory conditions, further unifying these diseases [10]. Interleukin-1 (IL-1) production on the other hand is induced in response to inflammatory stimuli and mediates various physiologic responses including inflammatory and immunological responses, responsible for the disease presentation. This would explain the presence of the features of both inflammatory and immunological responses in our case and efficacy of IL-1 receptor blockade in preventing relapsing fever and GN. Despite this, our case did not fit any of the known PFS. There are only several reports of vasculitides including Henoch–Schönlein purpura [11] and polyarteritis nodosa [12] in patients with Familial Mediterranean Fever. However, a relapsing kidney manifestation with reversible nephritic features was never described in any of the known PFS.

In conclusion, we presented a case of adult-onset IL-1-mediated PFS accompanied by acute relapsing GN with clinical features of severe AKI, hypocomplementemia, thrombocytopenia and nephrotic-range proteinuria followed by complete resolution of the symptoms and kidney function recovery after each episode. Kidney biopsies were delayed and revealed morphological features consistent with post-infectious GN. The nature of the condition is still not completely understood and needs further investigation.

Teaching points

(1) PFS could be associated with an acute nephritis with an unusual clinical presentation and morphological features of post-infectious GN.
(2) The main triggering mechanism for the disease appears to be related to autoinflammatory reactions with high fever and other signs of inflammation with no proof of preceding infection.
(3) Treatment with IL-1 receptor blockade was effective in preventing relapsing fever and associated GN.
(4) The nature of the PFS-associated GN is still not completely understood and needs further investigation.

Conflict of interest statement. None declared.

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