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CASES WITH A MESSAGE

C3 glomerulopathy in NLRP12-related autoinflammatory disorder: case-based review

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Abstract
Autoinflammatory diseases (AIDs) are a recently described group of conditions caused by mutations in multiple genes that code for proteins of the innate immune system. Cryopyrin-associated periodic syndromes (CAPS) are autoinflammatory diseases comprising three clinically overlapping disorders: familial cold urticarial syndrome (FCAS), Muckle–Wells syndrome (MWS), and neonatal-onset multisystem inflammatory disease (NOMID). CAPS have been associated with gain-of-function variations in *NLRP3* (NOD-like receptor family, pyrin containing domain-3). However, a new class of autoinflammatory disease resembling FCAS or MWS has been described in patients with *NLRP12* mutations. Here, we report a 6-year-old boy diagnosed with AID who developed an unexpected C3 glomerulopathy during attacks and carried a novel variation in *NLRP12*. Following treatment with IL (interleukin) 1 targeting agents, all symptoms and inflammation resolved. This is the first case in the literature affected by both autoinflammatory disease and C3 glomerulopathy.

Keywords Autoinflammatory disease · C3 glomerulopathy · NLRP12 · Pediatric

Introduction

Autoinflammatory diseases (AIDs) are a group of disorders characterized by recurrent episodes of fever and systemic inflammation that are sometimes complicated by amyloidosis [1, 2]. Among them is cryopyrin-associated periodic syndrome (CAPS), which comprises Muckle–Wells syndrome (MWS), familial cold induced autoinflammatory syndrome (FCAS), and the chronic infantile neurologic cutaneous articular syndrome (CINCA, also known as neonatal-onset multisystem inflammatory disease—NOMID). These three diseases have been associated with gain-of-function variations in *NLRP3* (NOD-like receptor family, pyrin containing domain-3), which is a member of NLR family (1). Patients with *NLRP12* (NOD-like receptor family, pyrin containing domain-12) variations and clinical manifestations compatible with CAPS have been described previously. Some authors described this disorder as a new class of autoinflammatory syndrome called *NLRP12*-associated disease [2, 3].

Herein, we report a 6-year-old boy diagnosed with AID, who developed an unexpected C3 glomerulopathy during attacks and carried a novel rare variation in *NLRP12*. To the best of our knowledge, this is the first case report in the literature that shows the association of *NLRP12* variation and C3 glomerulopathy in a patient with AID.

Case report

A 6-year-old boy was referred to our clinic with non-itching urticarial rash, fever, and fatigue. In his history, he had recurrent urticarial rashes on trunk and limbs that are accompanied by diarrhea and sometimes fever. Rashes and diarrhea

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lasted for 4–5 days. The patient had no family history of hereditary disorders. His mother had a history of recurrent urticarial rashes without any more clinical manifestation. On his laboratory examination, there were increased inflammatory markers with C-reactive protein (CRP) 7.3 mg/dl (normal 0–0.8 mg/dl), erythrocyte sedimentation rate (ESR) 84 mm/h, and white blood cell count 16,000 cells/mm^3. Urine analysis revealed hematuria (72 erythrocyte/hpf, hemoglobin +++) and proteinuria (spot urine protein to creatinine ratio: 0.54 mg/mg). Serum biochemistry and electrolyte levels were normal. On the 6th day of hospitalization, patient's symptoms improved spontaneously; and urinalysis and inflammatory markers returned to normal ranges without any treatment. 1 month after his discharge, he has admitted again with rash, fever, and tea-colored urine. CRP and ESR were high (6.5 mg/dl and 74 mm/h, respectively). He had hematuria (123 erythrocyte/hpf, hemoglobin +++) and proteinuria (17 mg/m^2/h). Laboratory investigation of electrolytes, rheumatoid factor, antinuclear antibody (ANA), liver and renal function tests, and complement components (C3 and C4) yielded normal results. In the follow-up period, he developed a severe headache; magnetic resonance imaging examination and lumbar puncture (L/P) confirmed the presence of intracranial hypertension (opening pressure 255 mmH_2O). He was treated with acetazolamide. Some further investigations were performed with a suspicion of AID. The audiometric investigation was normal. Serum immunoglobulin (Ig) D level was in normal ranges. There was no mevalonic aciduria based on the urine sample. An ophthalmological examination found bilateral papillary edema without any other ocular abnormalities. Skin biopsy showed nonspecific superficial perivascular infiltration with predominantly neutrophilic cells. Direct immunofluorescence was negative. On the 7th day of hospitalization, his renal function started to deteriorate. Serum creatinine was elevated to 1.81 mg/dl (normal 0.5–1.2 mg/dl) and blood urea was elevated to 94 mg/dl (normal 11–39 mg/dl). Serum complement levels decreased (C3 24.6 mg/dl, C4 9.9 mg/dl; normal ranges 83–177 mg/dl for C3 and 12–36 mg/dl for C4). ANA, anti-ds DNA, antineutrophil, and cytoplasmic antibody (ANCA) were still negative, while C1q and cryoglobulin levels were normal. A renal biopsy was performed. Light microscopy demonstrated segmental endocapillary proliferation and fibrinoid necrosis in 2 out of 13 glomeruli. Other glomeruli had mild glomerular basement membrane thicknesses. Immunofluorescence shows coarse granular C3 deposition. Electron microscopic examination revealed intramembranous, subendothelial, and subepithelial dense deposits. Findings suggested C3 glomerulopathy (Fig. 1). He was treated with intravenous methylprednisolone for 3 days (30 mg/kg/day) and continued with pulse cyclophosphamide (500 mg/m^2/month). He had a total of 6 months of pulse cyclophosphamide treatment. With this immunosuppressive therapy, his renal function tests and complement C3 level returns to normal ranges and no more proteinuria and hematuria were observed. Oral high-dose prednisone was tapered in 3 months and continued with 5 mg/alternate day. However, while on alternate day prednisone therapy, he was admitted again with fever, vomiting, and urticarial rashes on trunk and extremities (Fig. 2). His attacks were not triggered by any cold exposure. Inflammatory markers were high (CRP 11.9 mg/dl, ESR 97 mm/h). Unlike his previous attacks blood urea, creatinine, C3, C4, and urinalysis were normal. He had papillary edema on eye examination. L/P was performed and intracranial hypertension was detected again with an opening pressure of > 300 mm H_2O. Based on the patient's recurrent episodes of rashes, fever, intracranial hypertension, and high acute phase reactants, AID was suspected and anakinra was initiated (1 mg/kg/day, subcutaneously). Within 24 h, the skin rash disappeared and other symptoms also improved. In 15 days, CRP and ESR levels returned to normal values. Bilateral papillary edema was improved in the 1st month of the therapy and acetazolamide was stopped. Anakinra was later switched to canakinumab because of local pain and reaction at injection side. No disease flair (inflammatory and/or nephritis attack) was observed after 1 year of the therapy. Currently, he is on canakinumab (monthly, 2 mg/kg) therapy.

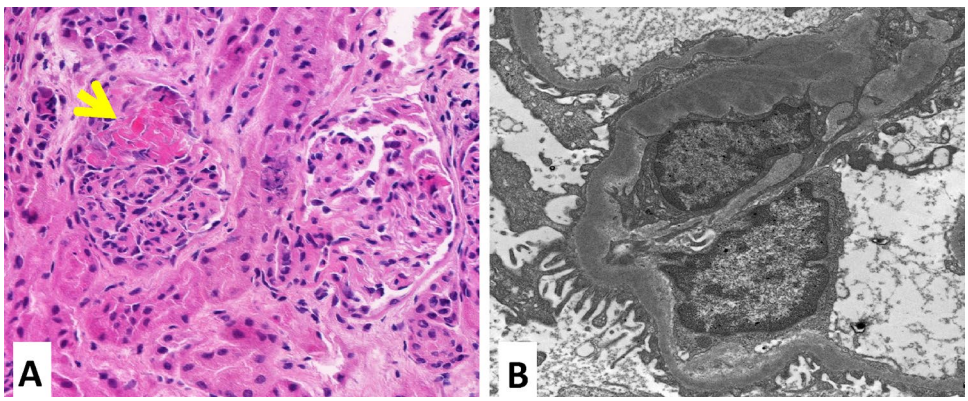

Fig. 1 **a** Two glomeruli in this view. Segmental fibrinoid necrosis is shown with yellow arrow (hematoxylin and eosin ×400). **b** Electron-dense deposits in intramembranous and subendothelial field (electron microscope ×7750)

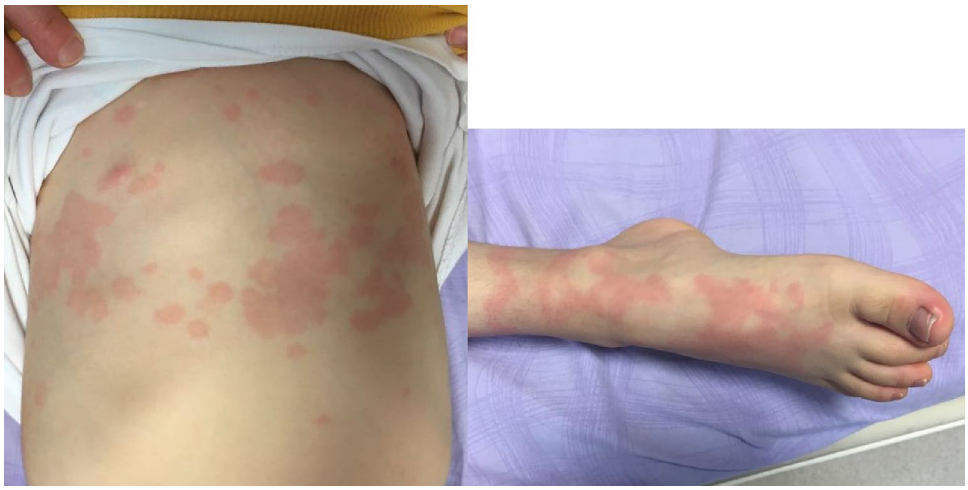

Fig. 2 Urticarial rashes of our patient with *NLRP12* variation on trunk and extremities

Genetic analysis

Genomic DNA was isolated from patient's peripheral blood sample using DNA Isolation Kit for Mammalian Blood (Roche Diagnostics, Mannheim, Germany) according to manufacturer's protocol. Patient's DNA was screened for coding and non-coding exons of the following 15 genes in IONS 5 platform (Life Technologies): *MEFV, MVK, TNFRSF1A, NLRP3, NOD2, CECR1, TMEM173, PSTPIP1, NLRP12, LPIN2, PLCG2, CARD14, SLC29A3, IL10RA*, and *NLRC4* using targeted New Generation Sequencing (NGS)-based panel designed by the Ion AmpliSeqTM designer software (Life Technologies). Variants of the patient were filtered mainly based on ANNOVAR tool [4], and disease associated or pathogenic variants were listed. Among above-mentioned genes, patient was found to carry a novel, rare variation in *NLRP12*, which is associated with FCAS. This missense variation, c.A1732G, p.S78G has not been reported before in other mutation databases (Table 1).

Search strategy

We performed a review of the literature using Pubmed and Web of Science between April and May 2018, combining the main keywords 'auto inflammatory' and 'NLRP12'. Results of the different databases were combined. We included full articles in English. We found eight articles discussing the cases having auto inflammatory disease and carrying *NLRP12* mutation (Fig. 3).

Discussion

Periodic fever syndromes are a group of AIDs characterized by recurrent episodes of fever and systemic inflammation [1, 2]. In our patient, the onset of the disease and symptomatology favor a diagnosis of FCAS. However, there are some overlapping features with MWS such as the duration of the episodes and with CINCA such as papillary edema and benign intracranial hypertension. On the other hand, he did not carry a *NLRP3* variation. Patients with clinical manifestations attributable to CAPS but without mutations in the *NLRP3* have been reported previously. Some of those *NLRP3* negative patients had *NLRP12* variations. Very few patients with *NLRP12*-related disease have been identified worldwide; therefore, there are limited data for the clinical presentation of this syndrome. *NLRP12*-related disease conditions were initially considered to be milder as compared to disorders caused by mutations in *NLRP3* [3, 5–9]. In 2008, Jeru et al. reported three affected children from two families with the features of hereditary periodic fever and carrying *NLRP12* mutations. Those patients' first symptoms started during the first year of life, episodes were triggered by exposure to cold and attacks (arthralgia, fever, and headache) lasted for several days. One patient had a distinguishing clinical manifestation with urticarial and sensorineural hearing loss [3]. In 2010, Borghini et al. described an Italian family in which some of the members had clinical features consistent with FCAS and had a missense mutation in *NLRP12*. They described the patients' manifestations as CAPS-like phenotype. They concluded that accelerated secretion of IL-1 beta and redox alterations was associated with this mild autoinflammatory disorder [6]. Later, in 2011, Jeru et al. added two more patients to their previous cases and named this phenotype as NLRP12-associated disorders [7]. Moreover, other patients with FCAS-like phenotype and *NLRP12* mutations have been reported in 2013, 2014, and 2016 [8, 10, 11]. In 2018, Kostik et al. reported a large single-center cohort discussing their *NLRP12*-related AID patients. They concluded that patients with *NLRP12* germline mutations demonstrated highly variable clinical phenotypes including immune deficiency syndromes. They

Table 1 Demographic and clinical features of patients with NLRP12 variation in the literature

	Patient 1 [3] (twin of patient 2)	Patient 2 [3] (twin of patient 1)	Patient 3 [3]	Patient 4 [6]	Patient 5 [6]	Patient 6 [6]	Patient 7 [6]	Patient 7 [7]	Patient 8 [7]	Patient no 9 [8]	Patient 10 [8]	Patient 11 [8]	Patient 12 [8]	Patient in this paper
Mutation	P.Arg284X	P.Arg284X	p.Val-635ThrfsX12	p.Asp-294Glu	p.Asp-294Glu	p.Asp-294Glu	p.Asp-294Glu	p.Arg-352Cys	p.Arg-352Cys	c.1223G>A p.W408X	c.1223G>A p.W408X	c.1223G>A p.W408X	c.1223G>A p.W408X	c.A1732G, p.S78G
Gender	M	M	F	F	M	F	M	Undetermined	Undetermined	F	F	M	M	F
Age	10 years	10 years	9 years	32 years	61 years	78 years	67 years	Undetermined	Undetermined	65 years	35 years	37 years	10 years	6 years
Age at onset of attacks	Newborn	Newborn	< 1 year	20 years	Undetermined	< 1 year	Undetermined	1 year	2.5 years	9 years	5 years	6 years	7 years	2 years
Duration of attacks	2–10 days	2–10 days	7 days	7–15 days	< 1 day	< 1 day	Undetermined	2–3 days	< 1 day	12–24 h	12–24 h	12–24 h	12–24 h	4–5 days
Fever	(+)	(+)	(+)	(+)	(−)	(+)	(+)	(+)	(+)	(+)	(+)	(+)	(+)	(+)
Abdominal pain	(−)	(−)	(+)	(−)	(−)	(−)	(−)	(+)	(+)	(−)	(−)	(−)	(−)	(+)
Cutaneous	Urticaria	Urticaria	(−)	Urticaria	Urticaria	Urticaria	Urticaria	(−)	Malar rash	Urticaria	Urticaria	Urticaria	Urticaria	Urticaria
Lymphadenopathy	(−)	(−)	(+)	(−)	(−)	(−)	(−)	(−)	(+)	(−)	(−)	(−)	(−)	(−)
Musculoskeletal	Arthralgia	Arthralgia	Arthralgia	Myalgia	Myalgia	Myalgia Arthralgia	(−)	Myalgia	Myalgia	(−)	Arthralgia	Arthralgia	(−)	Myalgia
Sensorineural hearing loss	(+)	(+)	(−)	(−)	(−)	(−)	(−)	(−)	(−)	(−)	(−)	(−)	(−)	(−)
Neurological	Headache	Headache	Rarely headache	Headache	(−)	(−)	(−)	(−)	(−)	(−)	(−)	(−)	(−)	Headache Pseudotumor cerebri
Eye	(−)	(−)	(−)	(−)	(−)	Optic neuritis	(−)	(−)	(−)	(−)	(−)	(−)	(−)	Papillary edema
Triggering agents	Cold	Cold	Cold	Cold	Cold	Cold	(−)	Cold	Cold	Cold	Cold	Cold	Cold	(−)
Aphthous stomatitis	(−)	(−)	(+)	(−)	(−)	(−)	(−)	(−)	(−)	(−)	(−)	(−)	(−)	(−)
Renal	(−)	(−)	(−)	(−)	(−)	(−)	(−)	(−)	(−)	(−)	(−)	(−)	(−)	C3 glomerulopathy

F female, *M* male

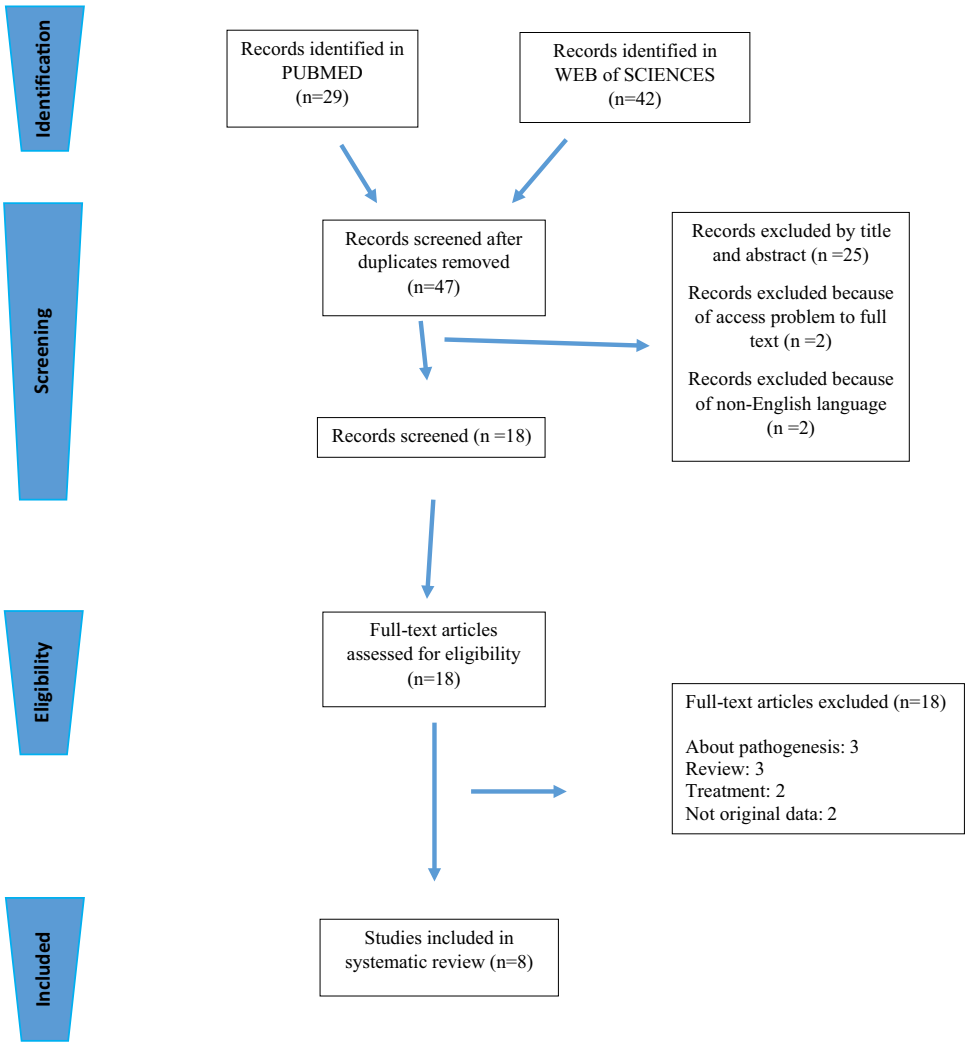

Fig. 3 Study flowchart

also observed an association between genetic diagnosis of *NLRP12*AID and increased susceptibility to infections was observed (9).

Distinct from other reported cases with *NLRP12* mutation, our patient had C3-GN and hematuria during his attacks. In the literature, patients with AID usually had renal involvement due to secondary amyloidosis that can be prevented by suppressing the excessive inflammation [12]. Pauci-immune crescentic GN has been reported in a patient with hyperimmunoglobulinemia D and periodic fever syndrome (HIDS) in 1999; however, the causal association was unclear. They hypothesized that the glomerular involvement was secondary to the cytokine network activation observed in HIDS [13]. In 2007, an 18-month-old boy presented with severe mevalonate kinase deficiency and membranoproliferative glomerulonephritis was reported. He was treated successfully with anakinra [14]. In 2011, Tsapenko et al. reported an adult male with recurrent mesangial and endocapillary proliferative GN and having frequent recurrent febrile illness which improved after treatment with rituximab and long-term anakinra therapy. In his attacks, he had severe acute kidney injury, hypocomplementemia, thrombocytopenia, and nephrotic range proteinuria followed by complete resolution of symptoms after each episode. This case has no mutation analysis and did not fit any of the known periodic fever syndromes. Authors concluded that the recurrent episodes with complete resolution and successful therapy with anakinra supported that the patient has an unknown periodic fever syndrome [15]. In 2016, a review article discussed the role of NLRP3 inflammasome in kidney diseases. NLRP3 inflammasome has been implicated in pathogenesis of some renal conditions including acute kidney injury, chronic kidney disease, diabetic nephropathy, and crystal related nephropathy. Inflammasome activation occurs in some kidney cells such as renal tubular epithelium [16].

C3 glomerulopathy is a rare disorder characterized at renal biopsy by C3 deposition, alone or with scanty immunoglobulins, as well as by an electron-dense material in mesangium, subendothelial, and subepithelial spaces. An abnormal systemic activation of the alternative pathway

(AP) of the complement cascade is responsible for the development of the disease if triggered by several possible environmental conditions. In 2016, Alexander et al. reported that an autoimmune milieu may act as a trigger for the development of C3 glomerulopathy in genetically susceptible patients. They also speculated that short-term prognosis of this disease associated with autoimmune disorders appears excellent [17]. In our patient, the exact etiology of a C3 glomerulopathy was not clear. His autoinflammatory disorder, excessive inflammation, and cytokine activation might serve as a trigger and lead to dysregulation of the alternative complement pathway. However, the nature of the condition is still not completely understood. Further investigation and new case reports are needed.

In conclusion, this is the first case in the literature that shows the association of an NLRP12-related AID and C3 glomerulopathy. Patients with NLRP12 variations may demonstrate variable additional clinical manifestations. It should be kept in mind that periodic fever syndromes may be accompanied with renal involvement.

Author contributions All authors made substantial contributions to conception and design of the paper as well as participated in drafting the article. All authors gave the final approval of the version to be submitted and any revised version. Study concept and design: ÖB and USB, NU. Analysis and interpretation of data: ÖB, FA, ETT, and SK. Drafting of the manuscript. ÖB, FA, ETT, and SK. Critical revision of the manuscript for important intellectual content: USB and ÖB. Study supervision: NÇ, USB, and NU.

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Compliance with ethical standards

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from the patient described in the case report. Parents of our patient have also agreed on publishing the pictures included in this manuscript.

Conflict of interest Authors declare that there is no conflict of interest.

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