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CASE REPORT

The case of a patient with familial cold autoinflammatory syndrome-2 caused by the *NLRP12* mutation associated with severe polyarthritis

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ABSTRACT

Familial cold autoinflammatory syndrome-2 (FCAS2) is a rare autosomal dominant disorder caused by pathogenic variants in the *NLRP12* gene. It is characterized by recurrent non-pruritic urticaria, arthritis, fever, and elevated inflammatory markers, often triggered by cold exposure. Here, we describe a Polish patient with FCAS2 linked to the *NLRP12* c.1054C>T (p.Arg352Cys) variant, who developed severe polyarthritis mimicking juvenile idiopathic arthritis (JIA), yet without fever. Urticarial rashes began at 8 months of age and were initially unrelated to cold, but later became cold-induced. Standard therapies with antihistaminic drugs for urticaria and methotrexate for JIA were ineffective. Due to persistent arthritis and high inflammatory markers, anti-IL-1 therapy (anakinra) was initiated, leading to marked clinical and laboratory improvement, confirming the autoinflammatory mechanism. This case broadens the knowledge of NLRP12-related syndromes and underlines the value of genetic testing in atypical arthritis unresponsive to standard treatment.

KEY WORDS:
familial cold autoinflammatory syndrome-2, ***NLRP12*****, polyarthritis.**

INTRODUCTION

Familial cold autoinflammatory syndrome-2 is an autoinflammatory disorder characterized by episodic and recurrent non-pruritic urticaria, arthritis, chills, fever, myalgia, and elevated serum inflammatory markers [1]. Cold exposure has been reported to trigger episodes in most, but not all patients [2–4]. Additional features may include abdominal pain, diarrhoea, headaches, nausea, thoracic pain, and neurosensory hearing loss. Familial cold autoinflammatory syndrome-2 is inherited in an autosomal dominant pattern with incomplete penetrance [5]. The age of symptom onset is variable, ranging from the first year of life to middle age [6]. Based on more than 60 reported cases in the literature, the severity and clinical manifestations of this condition appear to be heterogeneous [7]. Cases associated with *NLRP12* gene pathogenic variants in rheumatology/immunology practice in Poland are very rare, and to the best of our knowledge, only one case has been reported so far [8]. Here, we present the case of a patient with recurrent urticarial rashes induced by cold, without fever but with severe polyarthritis resembling juvenile idiopathic arthritis (JIA). Given the rarity of known *NLRP12* mutations, a detailed clinical description of another patient with a pathogenic variant of the *NLRP12* gene helps to delineate the clinical spectrum of NLRP12-associated inborn errors of immunity.

CASE REPORT

Our patient was the second child (girl) born to healthy, unrelated parents, delivered spontaneously at 40 + 4 weeks

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of gestation, with a birth weight of 4410 g and an Apgar score of 10/10. She has an older, healthy brother. The family history was affected by multiple sclerosis and autoimmune thyroiditis in the mother, psoriasis in the maternal grandfather, and allergy in the father. The child was healthy at birth and until 7 months of age. At 8 months of age, she developed generalized urticaria. She was treated with antihistaminic drugs, but without any clinical effect. The patient was referred to our hospital for skin changes at 12 months of age. Her developmental progress was appropriate for age, with timely achievement of developmental milestones, and no deficits in growth or body weight were observed. Urticarial changes on the skin faded under pressure, merging into erythematous lesions on the upper and lower limbs, followed by the face and trunk, without itching and with a slightly increased temperature. Skin changes worsened in the evening, after physical exertion, skin-to-skin contact, and crying. Laboratory tests revealed elevated C-reactive protein (163.8 mg/l, normal values: 0–10 mg/l) and amyloid A (432 mg/l, normal values: 0–6.4 mg/l) levels. She did not have fever at that time. Blood morphology and procalcitonin levels were within normal limits. Microbial testing revealed no pathogens, and the allergy panels were negative. Immunological tests revealed no abnormalities in the serum immunoglobulin (G, A, M, and D) and complement (component C3 and C4) concentrations. Flow cytometry analysis revealed normal percentages and absolute numbers of T-, B-, and NK-cells. Chemiluminescence analysis was used to verify the respiratory burst of neutrophils, and the results were within normal limits. No autoantibodies (ANA or ANCA) were observed. The laboratory test results, including humoral and cellular immunity parameters, performed in the patient at the age of approx. 4.5 years are shown in Table 1. The results of the genetic test for mastocytosis were negative. Skin biopsy revealed late-stage urticarial vasculitis. She was positive for HLA-B27 and HLA-Cw6 antigens, however, their clinical significance in her case remains unclear. No psoriatic skin or nails changes were observed. Regarding HLA-B27, it is present in 60–80% of patients with juvenile spondyloarthropathies (JSpA), yet only 1–5% of carriers develop the disease [9]. Juvenile spondyloarthropathies typically manifest in childhood (usually above 6 years old) or early adulthood, most often with peripheral arthritis of the lower limbs or asymmetric involvement of the hip, knee, or ankle joints [10]. Treatment, according to current recommendations, includes short-term glucocorticoids for high disease activity or complications, as well as disease-modifying antirheumatic drugs such as methotrexate or sulfasalazine [11]. We introduced such a therapy without satisfactory clinical effect. Therefore, the diagnosis of JSpA was unlikely, and the decision was made to treat the patient with the anti-IL-1 agent instead of tumour necrosis factor inhibitors. Genetic analysis (whole-exome sequencing) revealed a substitution c.1054C>T in exon 3 of the *NLRP12* gene, which causes an amino acid change from arginine to cysteine at position 352 p.(R352C). This genetic variant occurs at CpG sites and is localized in exon 3, which encodes the nucleotide-binding site (NBS) of the protein, crucial for NLRP12 function [12, 13]. Previous functional studies demonstrated that the p.Arg352Cys *NLRP12* variant is associated with a gain of function of caspase 1 processing and IL-1 secretion [14]. Since there was no effect of antihistamines, the patient received systemic steroids (prednisone, 2 mg/kg body weight) with improvement. The second episode of skin lesions occurred at the age of 3 years. Again, she received prednisone (1 mg/kg body weight) and presented a good clinical response. Since then, she has had periodic rashes after exposure to cold, without fever. At the age of 4 years, she was admitted to the hospital for polyarthritis. Ultrasound examination revealed effusions with synovial hypertrophy and increased blood flow in both knees and ankle joints, as well as effusions without synovial hypertrophy in the hip, elbow, and right wrist joints. Laboratory tests revealed elevated acute-phase proteins, high amyloid A levels (74 mg/l), and negative results for rheumatoid factor, anti-CCP, and ANA antibodies. All microbial tests detecting viruses (HCV, HBV, HIV, EBV, CMV, SARS-CoV2) and bacteria (*Streptococcus pyogenes, Borrelia, Yersinia, Salmonella, Shigella, Campylobacter, Chlamydia, Mycoplasma*) were negative. She received clindamycin, systemic and local steroids, and shortly thereafter, methotrexate, with no improvement on ultrasound examination. After adenotonsillectomy, the patient has started anti-IL-1 therapy with anakinra. Improvements in clinical status, laboratory parameters, and ultrasound images of the joints were achieved and persist to date. The treatment timeline, illustrating both the administered doses and the duration of each pharmacological agent received by the patient since the onset of arthritis, is presented in Figure 1. Currently, the patient is an active school-aged girl, with anthropometric parameters – percentile ranks for height, weight, and body mass index, of 57, 72, and 74, respectively.

CONCLUSIONS

The *NLRP12* gene encodes a protein that plays a key role in regulating the inflammatory response by controlling the activity of the inflammasome and signalling pathways, such as NF-κB and MAPK. The protein acts as both a negative and positive regulator of the immune response, depending on the context and stimulus [15]. According to the VarSome database, a heterozygous *NLRP12* missense mutation (c.1054C>T (p.Arg352Cys) (rs199881207) has been described in nine patients, including one patient from Poland [16]. The detailed clinical characteristics of the patients harbouring the genetic variant *NLRP12* c.1054C>T are presented in Table 2. However, clinical data are lacking for most of the patients. All patients described so far presented with high recurrent

TABLE 1. The patient's laboratory test results, including blood morphology and humoral and cellular immunity parameters, after the diagnosis of arthritis (patient at approx. 4.5 years old)

Analysed parameter	Patient's results	Age-matched reference values
Blood morphology		
WBC [cells/µl]	7600	4860–13 180
NEU [cells/µl]	2200	1300–7200
NEU (%)	24.7	16.9–74.0
LYM [cells/µl]	5800	1500–8100
LYM (%)	65.6	27.4–79.9
MONO [cells/µl]	700	300–1100
MONO [%]	7.8	3.8–12.8
EOS [cells/µl]	100	0.0–600
EOS (%)	1.2	0.0–3.2
BASO [cells/µl]	0.0	0.0–100
BASO (%)	0.5	0.0–0.6
Ig [cells/µl]	20	0.0–140
Ig (%)	0.2	0.0-0.9
RBC [cells/µl]	4 310 000	3 970 000–5 010 000
HB [g/dl]	11.6	10.2–12.7
HCT (%)	35.9	30.90–37.90
MCV [fL]	83.3	71.3–82.6
MCH [pg]	26.9	23.2–27.5
MCHC [g/dl]	32.3	31.9–34.2
PLT [cells/µl]	276 000	150 000–450 000
RDW-SD [fL]	41.9	34.9–42.4
RDW-CV (%)	13.8	12.7–15.1
PDW [fL]	13.2	–
MPV [fL]	11.3	8.9–12.4
P-LCR (%)	33.9	–
NRBC [cells/µl]	0	–
NRBC (%)	0	–
Serum immunoglobulins [g/l]		
IgG [IU/ml]	10.70	5.31–14.03
IgA [IU/ml]	1.27	0.31–1.92
IgM [IU/ml]	1.37	0.39–1.93
IgE [IU/ml]	199.00	0.00–60.00
C3c [g/l]	1.80	0.86–1.66
C4 [g/l]	0.34	0.13–0.32
RF [IU/ml]	< 9.88	0.00–20.00
CRP [mg/l]	163.8 (during episode); 10.4 (after episode)	< 10
ESR [mm]	86 (during episode); 24 (after episode)	< 10
SAA [mg/l]	432 (before anti-IL-1 treatment) < 0.83 (during treatment)	< 6.40
Anti-CCP [RU/ml]	< 1.00	≤ 5 negative results > 5 positive results
Cystatin C [mg/l]	0.84	0.62–1.11
HLA-B27	Positive	
HLA-Cw6	Positive	

TABLE 1. Cont.

Analysed parameter	Patient's results	Age-matched reference values	
Lymphocyte subpopulations (% of lymph)/[cells/µl]		% of lymph	Cells/µl
WBC	7600		4860–13180
LYM	59.9/4550	18.1–68.6	1250–5770
CD3	82.0/3731	59.0–75.7	1439–3511
CD4	56.0/2548	31.1–49.6	807–2257
CD8	22.0/1001	16.6–28.5	468–1154
CD4/CD8 ratio	2.5	1.2–2.7	
CD19	14.0/637	14.9–26.9	454–1102
CD16/56	3.0/137	5.4–18.0	165–787
Lymphocyte proliferation responses to mitogens and anti-CD3 stimulation			
PHA	19	< 4 no response 4–9 weak response ≥ 10 correct response	
anti-CD3	20		
PWM	21		
Chemiluminescence	Present	Present	

anti-CCP – anti-cyclic citrullinated peptide antibody, BASO – basophils, C3 – complement component C3, C4 – complement component C4, CD – cluster of differentiation, CRP – C-reactive protein, EOS – eosinophils, ESR – erythrocyte sedimentation rate, HB – hemoglobin, HCT – haematocrit, HLA – human lukocyte antigen, Ig – immunoglobulin, LYM – lymphocytes, MCH – mean corpuscular hemoglobin, MCV – mean corpuscular volume, MONO – monocytes, NEU – neutrophils, NRBC – nucleated red blood cells, PHA – phytohemagglutinin, PLT – platelets, PWM – pokeweed mitogen, RBC – red blood cells, RDW-CV – red blood cell distribution width, coefficient of variation, RDW-SD – red blood cell distribution width, standard deviation, RF – rheumatoid factor, SAA – serum amyloid A, WBC – white blood cells

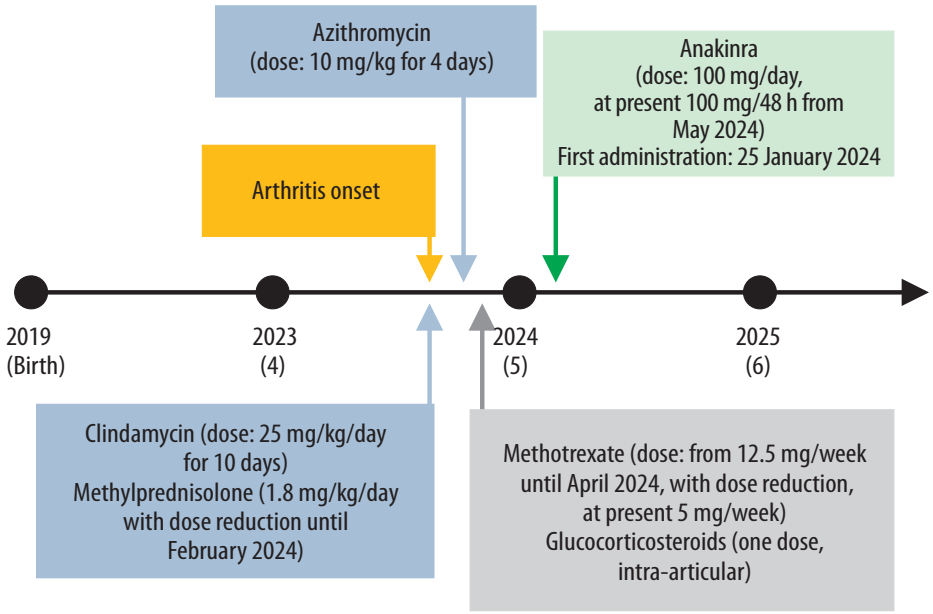

FIGURE 1. Treatment timeline, showing both the administered doses and the duration of each pharmacological agent received by the patient since the onset of arthritis

The child's ages, expressed in years, are indicated in brackets.

fevers typical of autoinflammation; however, our patient has not, even though she had increased levels of acute-phase proteins. Almost all patients, including ours, had skin changes triggered by cold exposure. Additionally, in patients with this specific mutation, compared to other *NLRP12* mutations, sensorineural hearing loss, visual impairment, neurological symptoms, and thoracic pain were not observed. Most patients suffered from joint pain, but only our patient had severe polyarthritis. Ultrasound images of inflamed joints suggested JIA due to the presence of effusions with synovial hypertrophy and increased blood flow. Typical treatment for JIA failed, and significant improvement was observed after the introduction of anti-IL-1 therapy. This finding suggests an autoinflammatory aetiology of arthritis. Since she has been treated with anakinra, no flare-ups of symptoms have been observed. At present, we are attempting to decrease the dose of anti-IL-1 drug under a strict control of clinical symptoms.

TABLE 2. Detailed clinical characteristics of patients described in the literature with the NLRP12 c.1054C>T (p.Arg352Cys) variant

Analyzed feature	Our patient	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8	Patient 9
Origin	Poland	Poland	Armenia	Italy	Russia	Italy, blood-related with Patient 6	Italy, blood-related with Patient 5	Russia	Russia	Turkey
Sex	Female	Female	No data	No data	Female	No data	No data	Male	Female	No data
Age at onset of attacks	1 year	Early childhood (not specified)	1 year	2.5 years	No data	No data	No data	No data	No data	No data
Triggering effect of cold	Yes	Yes	Yes	Yes	Yes	No data	No data	No data	No data	No data
Fevers	No	Yes (40°C) from the age of 17	Yes (40°C)	Yes (40°C)	Yes	No data	No data	Yes	Yes	No data
Abdominal pain	No	No data	Yes	Yes	Yes	No data	No data	No	Yes	No data
Thoracic pain	No	No data	No	No	No date	No data	No data	No date	No date	No data
Musculoskeletal signs	Severe polyarthritis	Arthralgia and myalgia	Myalgia	Myalgia	Arthralgia	No data	No data	No data	Arthralgia	No data
Lymphatic signs	No	No data	No	Adenopathy	Splenomegaly	No data	No data	No data	Splenomegaly	No data
Cutaneous manifestations	Urticarial rash	Urticaria-like lesions	No	Malar rash	Episodic urticarial-like rash	No data	No data	Atopic dermatitis	Urticarial rash	No data
Sensorineural hearing loss	No	No data	No	No	No data	No data	No data	No data	No data	No data
Visual impairment	No	No data	No	No	No data	No data	No data	No data	No data	No data
Neurologic manifestations	No	No	No	No	No data	No data	No data	No data	No data	No data
Proteinuria/amyloidosis	Amyloidosis	No	No	No	No data	No data	No data	No data	No data	No data
CRP level	High	No data	No data	70	High level of CRP	No data	No data	Elevated CRP	Elevated CRP	No data
Other signs	No	Headaches	No data	Buccal aphthosis	Failure to thrive, growth delay	No data	No data	Chronic rhinitis	Elevated ESR	No data
Treatment/effect of treatment	MTX – no effect; Anakinra – very good effect	Tocilizumab combined with mycophenolate mofetil and plasmapheresis	No data	No data	Canakinumab	No data	No data	No data	No data	No data
Reference		Cichoń *et al.* [8]	Jéru *et al.* [14]	Jéru *et al.* [14]	Kostik *et al.* [17]	Vilariño-Güell *et al.* [18]	Vilariño-Güell *et al.* [18]	Suspitsin *et al.* [19]	Suspitsin *et al.* [19]	Bozgeyik *et al.* [20]

Our patient is marked in grey.
CRP – C-reactive protein, ESR – erythrocyte sedimentation rate, MTX – methotrexate

DISCLOSURES

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4. Conflicts of interest: None.
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REFERENCES

1. Poli MC, Aksentijevich I, Bousfiha AA, Cunningham-Rundles C, Hambleton S, Klein C, et al. Human inborn errors of immunity: 2024 update on the classification from the International Union of Immunological Societies Expert Committee. J Hum Immun 2025; 1: e20250003.
2. Tanaka N, Izawa K, Saito MK. Familial cold autoinflammatory syndrome. In: GeneReviews®. University of Washington, Seattle 1993–2024.
3. Hoffman HM, Broderick L. The role of the inflammasome in patients with autoinflammatory diseases. J Allergy Clin Immunol 2016; 138: 3-14.
4. Aksentijevich I, Masters SL. Autoinflammatory diseases: an update on diagnosis and treatment. Curr Opin Rheumatol 2016; 28: 511-519.
5. Borghini S, Tassi S, Chiesa S, Caroli F, Carta S, Caorsi R, et al. Clinical presentation and pathogenesis of cold-induced autoinflammatory disease in a family with recurrence of an NLRP12 mutation. Arthritis Rheum 2011; 63: 830-839.
6. Shen M, Tang L, Shi X, Zeng X, Yao Q. NLRP12 autoinflammatory disease: a Chinese case series and literature review. Clin Rheumatol 2017; 36: 1661-1667.
7. Del Porto F, Cifani N, Proietta M, Verrecchia E, di Rosa R, Manna R, et al. NLRP12 gene mutations and auto-inflammatory diseases: ever-changing evidence. Rheumatology (Oxford) 2020; 59: 3129-3136.
8. Cichoń M, Zielińska P, Zaucha JM, Zarzycka E, Trzeciak M. Cold-induced urticaria-like lesions related to NLRP-12 mutation. J Eur Acad Dermatol Venereol 2023; 37: e874-e876.
9. Gmuca S, Weiss PF. Juvenile spondyloarthritis. Curr Opin Rheumatol 2015; 27: 364-372.
10. Srinivasalu H, Sikora KA, Colbert RA. Recent updates in juvenile spondyloarthritis. Rheum Dis Clin North Am 2021; 47: 565-583.
11. Smolen JS, Landewé RBM, Bergstra SA, Kerschbaumer A, Sepriano A, Aletaha D, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2022 update. Ann Rheum Dis 2023; 82: 3-18. Erratum in: Ann Rheum Dis 2023; 82: e76.
12. Williams KL, Lich JD, Duncan JA, Reed W, Rallabhandi P, Moore C, et al. The CATERPILLER protein monarch-1 is an antagonist of toll-like receptor-, tumor necrosis factor alpha-, and Mycobacterium tuberculosis-induced pro-inflammatory signals. J Biol Chem 2005; 280: 39914-39924.
13. Ye Z, Lich JD, Moore CB, Duncan JA, Williams KL, Ting JP. ATP binding by monarch-1/NLRP12 is critical for its inhibitory function. Mol Cell Biol 2008; 28: 1841-150.
14. Jéru I, Le Borgne G, Cochet E, Hayrapetyan H, Duquesnoy P, Grateau G, et al. Identification and functional consequences of a recurrent NLRP12 missense mutation in periodic fever syndromes. Arthritis Rheum 2011; 63: 1459-1464.
15. Tuladhar S, Kanneganti TD. NLRP12 in innate immunity and inflammation. Mol Aspects Med 2020; 76: 100887.
16. Kopanos C, Tsiolkas V, Kouris A, Chapple CE, Aguilera MA, Meyer R, et al. VarSome: the human genomic variant search engine. Bioinformatics 2019, 35: 1978-1980.
17. Kostik MM, Suspitsin EN, Guseva MN, Levina AS, Kazantseva AY, Sokolenko AP, et al. Multigene sequencing reveals heterogeneity of NLRP12-related autoinflammatory disorders. Rheumatol Int 2018; 38: 887-893.
18. Vilariño-Güell C, Zimprich A, Martinelli-Boneschi F, Herculano B, Wang Z, Matesanz F, et al. Exome sequencing in multiple sclerosis families identifies 12 candidate genes and nominates biological pathways for the genesis of disease. PLoS Genet 2019; 15: e1008180. Erratum in: PLoS Genet 2020; 16: e1008737.
19. Suspitsin EN, Guseva MN, Kostik MM, Sokolenko AP, Skripchenko NV, Levina AS, et al. Next generation sequencing analysis of consecutive Russian patients with clinical suspicion of inborn errors of immunity. Clin Genet 2020; 98: 231-239.
20. Bozgeyik E, Mercan R, Arslan A, Tozkir H. Next-generation screening of a panel of genes associated with periodic fever syndromes in patients with Familial Mediterranean Fever and their clinical characteristics. Genomics 2020; 112: 2755-2762.