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NLRP12-Associated Autoinflammatory Diseases Such as Fcas2 Persisting Like Marshall Syndrome, A Case Report

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Introduction

Systemic Autoinflammatory Diseases (SAIDs) encompass a group of monogenic disorders characterized by periodic activation of inflammasomes, involving various pathogenic pathways such as heightened oxidative stress, autophagy, and pro-inflammatory cytokine storms (Wang, 2022; Lachmann, 2017; Krainer et al., 2020; Kacar et al., 2019). Examples of SAIDs include familial Mediterranean fever (FMF) and Tumor Necrosis Factor Receptor-Associated Periodic Syndrome (TRAPS) (Ancient missense mutations in a new member of the Roret gene family are likely to cause familial Mediterranean fever. The International FMF Consortium, 1997; McDermott et al., 1999). This spectrum comprises over 30 pathologic entities with diverse pathogenic genes (Wang, 2022).

Among the pathogenic genes associated with SAIDs is the Nucleotide-binding Leucine-rich Repeat-containing Receptor 12 (NLRP12) gene (Tuladhar & Kanneganti, 2020). NLRP12 plays a crucial role in regulating the innate immune system, and its loss of function results in increased activation of innate immunity (Tschopp et al., 2003). This condition is characterized by the excessive secretion of pro-inflammatory cytokines, particularly triggered by cold exposure, leading to its designation as Familial Cold Autoinflammatory Syndrome 2 (FCAS2) (Jéru et al., 2011). FCAS2 commonly initiates in childhood and poses challenges in diagnosis, particularly in the pediatric population (Borghini et al., 2011). The purpose of this study is to present a case of FCAS2, aiming to enhance our understanding of its presenting signs and symptoms, as well as the diagnostic course with a novel mutation in NLRP12 gene.

Case Presentation

The patient, a four-year-old boy and one of two non-identical twins (Di-Chorionic, Di-Amniotic), was born to non-consanguineous parents with a history of recurring high fever (> 40°C) since he was six months old. The patient who had been hospitalized several times due to febrile episodes and adenitis, pharyngitis, and aphthous ulcers. He has had persistent elevated C-reactive protein in his admissions. With the diagnosis of Periodic Fever, Aphthous stomatitis, Pharyngitis, Adenitis (PFAPA, Marshall Syndrome), the patient received Prednisolone (just in attack), Cetirizine, Montelukast, and Colchicine. This regimen shortened the febrile episodes, but the complaint persisted. During febrile episodes, the patient reported experiencing headaches and arthralgia in his lower extremities, occasionally accompanied by abdominal pain.

He was referred to our clinic for evaluation of periodic fever. During the initial assessment, the patient presented with a fever of 40.2°C, a pulse rate of 102 bpm, and a respiratory rate of 23 rpm. Blood pressure was normal, and oxygen saturation on room air was 99%.The patient has adenitis, pharyngitis, and aphthous ulcers. The patient exhibited irritability, bilateral cervical lymphadenopathy, but no focal neurologic deficits. Meningeal signs (Kernig and Brudzinski) were negative, and he had normal vision in both eyes (Visual acuity of 20/20). No evidence of arthritis was noted during the examination. Normal bowel habits, normal bowel sounds, and the absence of abdominal tenderness or organomegaly were observed during the physical examination.

Laboratory studies revealed elevated CRP and ESR, along with signs of Rouleaux formation in the peripheral blood smear. Assessment of antibodies showed relatively high IgE levels, while other hematologic and immunologic lab studies returned normal results. Due to the complaint persisted Whole exome sequencing was done and identified a heterozygote mutation in the NLRP12 gene, specifically c.2927+2T>C on intron 8/9 (Chr19 (hg38):g53798241). Sanger sequencing confirmed this mutation. Family segregation study revealed the same mutation in the patient's mother. Table 1 provides a summary of the patient's other lab studies.

Low-dose prednisolone and Anakinra was started for the patient which ended in decreased frequency and severity of the febrile attacks. While the patient used to experience fever every two weeks, the initiation of Prednisolone and Anakinra increased the fever-free intervals to 3 months.

Table 1: laboratory studies of the patient

Parameter	Reference range	October 5th 2020	August 3rd 2021	October 2nd 2023
WBC (/µL)	4300-11000	6,100	4,470	11,490
Myelocyte (%)		1		
Neutrophils (%)		38	28.0	65
Eosinophils (%)		2	2.9	1
Lymphocytes (%)		36	57.2	15
Monocytes (%)		16	8.7	12
Band cells (%)		7	3.0	6
Basophils (%)		0	0.2	1
Hemoglobin (g/dL)	13.5-18	10.4	11.7	11.2
Platelet (/µL)	150,000-450,000	289,000	373,000	310,000
PBS		Moderate toxic granulation, mild hypochromia, mild microcytosis	Slight anisocytosis, slight hypochromia, few elliptocytes	1+ Anisocytosis, 2+ Rouleaux formation
ESR (mm/hr)	Age/2	84	10	
CRP (mg/L)	<6	192	1	
Fibrinogen (mg/dL)	200-400		285	
Blood urea nitrogen (mg/dL)	8-23		13	
Creatinine (mg/dL)	0.03-0.50		0.44	
Uric Acid (mg/dL)	3.6-8.2		3.7	
Triglycerides (mg/dL)	<150		195	
Calcium (mg/dL)	9-12		10.4	
Phosphorus (mg/dL)	4-7		6.1	
AST (U/L)	15-60		35	
ALT (U/L)	<42		16	
ALP (U/L)	180-1200		732	
LDH (U/L)	225-450		405	
Serum Iron (µg/dL)	40-168		81	
Ferritin (ng/mL)	7-140		24.30	
IgG (mg/dL)	295-1156		621	
IgA (mg/dL)	27-79		50	
IgM (mg/dL)	37-184		73	
IgE (IU/mL)	<97		130	
RF (IU/mL)	<20		3.1	
Wright agglutination (titer)	<1:160		Negative	
Widal Agglutination (titer)	<1:80		Negative	
2-ME (titer)			Negative	
ANA (U/mL)	<0.8		0.3	
TSH	0.27-5.95		2.56	
Influenza A PCR				Negative
Influenza B PCR				Negative
SARS-CoV-2 PCR				Negative

Discussion

In this case report, we detail the presentation of a patient with Familial Cold Auto inflammatory Syndrome 2 (FCAS2), characterized by periodic fever, headache, and cervical lymphadenopathy. Notably, a novel mutation in the NLRP12 gene was identified. The patient exhibited heterozygosity for this mutation, and the same genetic alteration was detected in his mother, highlighting the autosomal dominant nature of the disease with variable penetration.

Our patient began experiencing periodic fevers at six months old, coinciding with the decline of maternal antibodies and the activation of the infant's humoral immune system. Additionally, the patient presented with elevated IgE levels, suggesting that the NLRP12 mutation may have exerted enhancing effects on the innate immune system, subsequently triggering the activation of the humoral immune system.

In a case report by Jeru et al., the authors presented two patients with NLRP12-associated auto inflammatory disorder who exhibited periodic fever and urticaria, along with symptoms of headache and sensorineural hearing loss. The patients displayed elevated C-reactive protein (CRP) levels during febrile episodes. The study revealed heightened spontaneous IL-1β secretion in these patients, accompanied by significantly increased serum levels of IL-6, while TNF-α levels remained close to normal. When exposed to lipopolysaccharide, the patients' peripheral mononuclear cells exhibited an induced secretion of IL-1β, IL-6, and TNF-α at levels 5-6 times higher than expected in normal participants. This suggested a diminished baseline immune regulation and impaired downregulation of the antimicrobial effects of mononuclear cells. The authors initiated treatment with Anakinra (Anti-IL-1), observing an initial positive response with decreased IL-1β secretion. However, after three months of treatment, the patients developed severe myalgia, and the febrile attacks returned. This adverse outcome could potentially be attributed to an increase in other cytokines. As a result, the authors concluded that targeting only one aspect of the innate immune response may not be a sufficient therapeutic approach (Jéru et al., 2011). They suggested that broad immunomodulation with corticosteroids could be a more effective choice, a perspective also supported by similar observations in our case.

Approximately 30 cases of pediatric NLRP12-associated autoinflammatory disorder (NLRP12-AD) have been reported to date, with a male-to-female ratio of about 1:1.9. In all these cases, periodic fever was a consistent symptom. Less frequent clinical presentations included arthralgia, abdominal pain, dermatologic rash (mostly urticaria), and lymphadenopathy (Havnaer & Han, 2019). The relatively nonspecific nature of these manifestations makes diagnosis challenging, and genetic studies, such as whole exome sequencing, play a pivotal role in confirming the condition. The most prevalent mutation in this disorder has been identified as c.1206C>G; however, our study encountered a novel mutation (c.2927+2T>C) that had not been previously reported (Wang, 2022; Wang et al., 2002; Kostik et al., 2018). This emphasizes the genetic heterogeneity within the disorder and underscores the importance of comprehensive genetic analyses for accurate diagnosis, especially when faced with atypical clinical presentations.

In a case report by Ghosh et al., a nine-year-old male patient was documented with recurrent fever (below 38°C), abdominal pain, and joint hyperlaxity. Neutrophilia and elevated CRP were observed during the episodes, but no eosinophilia was detected. Immunoglobulin levels were within the normal range, and the patient exhibited a relative response to Naproxen and a short-course of prednisolone (Ghosh et al., 2019). In contrast, our case involved elevated IgE levels, indicating the variability in the presentation of this disease. It is noteworthy that this condition may manifest in diverse ways. While it would be beneficial to investigate cytokines related to eosinophil growth and development, such as IL-3 and IL-5, this was not feasible in our center. This disparity in clinical presentations emphasizes the need for a comprehensive understanding of the varied manifestations of NLRP12-associated autoinflammatory disorder. The exploration of different clinical profiles enhances our ability to recognize and manage the condition effectively, taking into account the heterogeneity in its expression.

In a case report by Yang et al., a nine-year-old girl initially presented with persistent fever and arthritis affecting her knees and wrists. Elevated inflammatory markers, including CRP, ESR, serum ferritin, and IL-6, were observed. Initially misdiagnosed with juvenile idiopathic arthritis, she was treated with prednisolone, folate, and methotrexate. Tocilizumab injections were later introduced, effectively controlling her symptoms, although inflammatory markers remained elevated. Upon the resolution of symptoms, tapering prednisolone led to symptom recurrence. Whole exome sequencing revealed a mutation in NLRP12. Discontinuation of tocilizumab and an increase in prednisolone dosage resulted in improved symptom control (Yang et al., 2023). In our study, similar to the reported case, corticosteroids played a crucial role in achieving relative symptom control in our patient.

Conclusion

In summary, we presented a case of NLRP12-associated autoinflammatory disease characterized by periodic high fever bilateral cervical lymphadenopathy pharyngitis and adenitis. NLRP12-associated autoinflammatory diseases such as FCAS2 can present as PFAPA, and treatment targeted at PFAPA can ameliorate the condition. Notably, this case was associated with a novel mutation in the NLRP12 gene (c.2927+2T>C). This adds to the growing understanding of the genetic heterogeneity within the spectrum of NLRP12-associated autoinflammatory disorders and underscores the importance of genetic studies in accurate diagnosis and management.

Abbreviations

Systemic Autoinflammatory Diseases (SAIDs)
Familial Cold Autoinflammatory Syndrome 2 (FCAS2)
Nucleotide-binding Leucine-rich Repeat-containing Receptor 12 (NLRP12)

Ethical Approval and Consent to Participate

The study has been approved by the committee of Ethics in Biomedical Research of Shiraz University of Medical Sciences by the code:IR.SUMS.MED.REC.1402.491 after obtaining a written consent form from the patient's parents.

Consent for Publication

A written consent form has been signed by the patient's parents for the data to be published anonymously.

Availability of Supporting Data

Not applicable.

Competing Interests

The authors declare that they have no competing interests.

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Authors' Contributions

All authors were involved in the treatment of the patient. The draft has been written by AA; and the contents of the manuscript has been approved by RZ SH and AA.

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