Successful Therapy in Cases Series of Systemic Autoinflammatory Disease and Literature Review

SHAOXIAN HU

Division of Rheumatology, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology

MEI YU

Division of Stomatology, Wuhan Municipal Hospital of Traditional Chinese Medicine, Wuhan, Hubei, China

XIAOWEI HUANG

Division of Digestive medicine, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, China

RUI XING

Division of Rheumatology, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology

YIKAI YU (✉ yuyikai@163.com)

Division of Rheumatology, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology

Research Article

Keywords: Systemic autoinflammatory disease (SAID), SAID patients, tofacitinib treatment, FMF

Posted Date: December 20th, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-1156651/v1>

License: © ⓘ This work is licensed under a Creative Commons Attribution 4.0 International License.

[Read Full License](#)

Abstract

Objectives: Systemic autoinflammatory disease (SAID) is a rare systemic auto-inflammatory and progressive disorders. There have been some reports with various therapies in SAID patients. The objective of this study is to describe the chareatercis of four cases of NAIDs benefiting from JAK 1/2 inhibitor baricitinib.

Methods: We reported the four cases with SAID including two cases of Blau syndrome, one case of FMF and one case of FCAS3 syndrome. These four different patients were either resistant to currently available therapies or biologics were unaccessible during COVID-19 pandemic. We also conducted a systematic literature review about the current therapies of SAID.

Results: Although genetically and phenotypically different, four cases of SAID that were treated with single use baricitinib 4 mg per day achieved improvement over eight weeks. We further identified 132 manuscripts providing more than 100 cases of SAID. Among these patients, 24 underwent biological treatments and 22 of them recovered. In these 132 manuscripts, 2 underwent JAK 1/3 inhibitor tofacitinib treatment and recovered fully.

Conclusions: Case series study on the use of Jak inhibitor agents have yielded positive results in our study. For SAID patients baricitinib may be a better choice compared to injection biological treatments.

Introduction

The term autoinflammatory disease was initially proposed by McDermott et al and published in the journal Cell in 1999 and was a spectrum of genetically heterogeneous inflammatory disorders(1). SAIDs are currently considered to be a cluster clinical disorders characterized by abnormally increased systemic inflammation, representing a spectrum of disease ranging from Mendelian disorders to genetically complex diseases.

SAIDs can also be of polygenic or multifactorial origin. Monogenic SAIDs are caused by highly penetrant genetic variants in mono genes and follow a typical pattern of Mendelian inheritance. The most common monogenic SAIDs have been described are familial Mediterranean fever (FMF), NLRP3-associatedautoinflammatory disease (cryopyrin associated periodic syndromes - CAPS), TNF receptor-associated periodic syndrome (TRAPS) and nucleotide-binding oligomerization domain 2 (NOD2) gene that are linked to Blau syndrome and FACS3. Papa et al. predesignated an NGS (next generation sequencing), diagnostic panel, including 41 genes related to SAIDs and additional genes reported in the INFEVERS database (2).

Using state-of-the-art molecular and genetic methodologies like NGS numerous genetic markers, some of which may be of diagnostic value have been identified. In SAIDs, digenic variants or combinations of more genetic variants in different genes can be detected and a particular of SAID may be related to the NOD2 genes which is located on 6th chromosome. Recently the prevalence of the common NOD2

variants has been well studied and documented in SAID populations. The mutations are likely to be disruptive and pathogenic, resulting in loss of structure or function variants of NOD2. These variants may contribute to heterogeneous phenotypes in an individual, complicating the diagnosis and therapy. These disorders may have overlapping clinical phenotypes and characterized by periodic fever, dermatitis, arthritis and gastrointestinal (GI) and sicca like symptoms and has a genetic association with NOD2 variants.

In this study, we followed up four newly diagnosed cases since last year with clinical manifestations at risk for SAID and extended study of the phenotypic and genotypic features of the cases treated with Jak inhibitors. The clinical and laboratory data were then classified according to the presence of NOD2 variants (Table 1).

Methods

We prospectively studied 4 cases of SAID between October 2019 and May 2020 in a cohort of 10 cases. Tests for different autoimmune disorders, neoplastic conditions and immunodeficiencies were negative. All patients with SAID to date have been Chinese Han ethnicity and while both sexes are affected without gender predominance.

The systematic PubMed search was conducted for the literature and was limited to publications in English between 1999 and Dec 2020, when the autoinflammatory disease was first reported, and the following keywords were applied: “autoinflammatory disease”, “Yao syndrome”, “systemic autoinflammatory syndrome”, “Blau syndrome”, “NOD2”, “PLCG2” and “FMF”. This research was approved by the Institutional Review Board, Tongji Hospital in Wuhan, according to the Declaration of Helsinki. Informed consent was obtained from all the patients.

Case-1

An 18-year-old girl was referred to Rheumatology Clinic in October 2019 for polyarthralgia and recurrent fevers. When 14 years old she was then noticed episodes of recurring high fever (38.5–40°C) with flulike symptoms (generalized aches and myalgia) and had disease flares once every month and each episode lasted for several days. At the age of 16, she also complained of recurrent abdominal pain. A computed tomography scan of the neck, chest, abdomen, and pelvis did not reveal any other lymphadenopathy. An infectious disease workup was negative. Routine blood tests such as complete blood count, complete metabolic panel were unremarkable, and urinalysis is with unexplained proteinuria (24-Hour Urine Protein 437mg). Further genetic testing was positive and heterozygous for the MEV1 NM_000243.2:c.2040 C>A (p.Met 680Ile) (Figure 1a) and was diagnosed as FMF. Because of the recurrent febrile episodes, the patient was administered colchicine 1.0 mg for a week then increased to 2.0mg daily but without benefits at all. The patient then was administered baricitinib 4mg daily with complete resolution of symptoms within three months. She remained afebrile at follow-up six months later.

Case-2

A 17-year-old immunocompetent boy was referred to Rheumatology Clinic in December 2019. He developed mild edema and pain of his wrists, knees, DIP and MCP joints at age of 3 when initially diagnosed with juvenile rheumatoid arthritis. He developed ichthyosis plaques on both cheeks (Figure 1b). The patient's father passed away due to traffic accident at the age of 40 and denial of any relevant disorders reported by patient's mother. There was no family history of similar conditions. At year of 14 after a routine school visual screening examination, his parent was notified that a formal ophthalmologic evaluation was needed. From then, he was confirmed as uveitis (Figure 1c) and needed tropicamide drops that act as mydriasis to keep his eye vision. And CBC showed normocytic anemia and serum cytokines profiles normal. Chest imaging, QuantiFERON-TB Gold test and HLA-B27 were within normal limits. Peripheral blood lymphocyte subset panel showed decreased slightly of natural killer cell. The genetic testing identified that the young patient carries a heterozygous genotype NM_02216 2.2:c.1000 C>T (p.Arg334Trp) of compound NOD2 variant which has been detected in sporadic Blau syndrome (Figure 1d). The diagnosis of Blau Syndrome was provisionally made and blood samples from the patient and his brother and mother were tested for known genetic mutations associated with Blau Syndrome, which turned out negative. The past medications also included adumumab for eight weeks for recurrent arthralgia and denial of corticosteroid. Due to COVID-19 pandemic in Wuhan, he had to stop injection for three months and within 3 months after administration of Baricitinib, uveitis has been in remission with a best-corrected visual acuity (BCVA) of 6/6, N6 in both eyes and arthritis resolved completely.

Case-3

A 17-year-old boy was referred to Rheumatology Clinic in January 2020 with a maculopapular erythematous rash over her upper extremity body. The patient's family history revealed similar inherited familial disease of. At age of 14 years old, the patient visited our clinic with swelling of the dorsum and camptodactyly of the hands (Figure 1e). Physical examination revealed swelling, pain, limitation of movement in both hands. The patient was diagnosed with juvenile idiopathic arthritis (JIA) and administered ibuprofen, prednisolone, and oral methotrexate, partial resolved. Hands erosion MRI (Figure 1f) revealed tissue oedema. Genetic studies showed a heterozygote mutation genotype NM_02216 2.4:c.912 C>T (p.Gly304Val) of compound NOD2 variant (Figures 1g). In silico assessment (SIFT, Mutation Taster, and Polyphen) of the mutation indicated a strong association with Blau syndrome. However, the patient developed fever 3 weeks after initiation of etanercept treatment, therefore the administration was ceased. Four months after treatment commenced, unpredictably COVID-19 pandemic broke out, we initiated treatment of baricitinib and reached full disease remission.

Case-4

A 23-year-old lady was referred to Rheumatology Clinic in May 2020. She presented with recurrent rash to cold temperatures and intermittent fever for 3 years. She has been suffering from polyarthritis in bilateral knees and ankle joints since the age of 12. Physical examination was remarkable overall rashes (Figure 1h). Laboratory investigation showed moderate anemia and normal white blood cell count. CT scan showed axillary lymphadenopathy and splenomegaly. IgG=4.32 g/L and B Lymphocyte subsets by flow

cytometry was as low as 3.0 % (Table-1). Genetic testing for the periodic fever syndrome genes (*MEFV*, *MVK*, *TNFRSF1A*, *NLRP3*) was normal. Heterozygous for the *PLCG2* sequence variants NM_002661.5:c.1940A>C (p.Tyr647Ser) (Figure 1i) was confirmed positive by NGS. Then the patient was diagnosed with Familial Cold Autoinflammatory Syndrome 3 (FCAS3) (3). She was initially given cetirizine and prednisone 40 mg per day, and the rash, fever episodes and polyarthritis improved partially. But prednisone could not be tapered below 30 mg daily due to deterioration of symptoms. Subsequently, she started with infliximab for 2 months and was then discontinued because fever got worsened. She remained on baricitinib for 3 months, fever and erythema nodosa accompanied with polyarthritis fully diminished.

Discussion

The clinical disorder of SAID was defined as episodes of seemingly unprovoked inflammation without high titer autoantibodies or antigen-specific T cells and mediated predominantly by the cells and molecules of the innate immune system with a significant host predisposition(4).

FMF is a most frequently common autosomal recessive monogenic SAID, and the Tel Hashomer criteria is the most widely used criteria for the diagnosis of FMF in adult patients. It includes a set of ten criteria grouped into Major criteria, Minor criteria, and molecular criteria which is associated with mutation of *MEFV* gene (5). *MEFV* is located on the chromosome 16p 13.3 and encoding the Pyrin protein. The first case patient underwent several treatments and was refractory to colchicine before beginning a regimen of baricitinib and reaching full disease remission. Tobon firstly reported FMF could be controlled by tofacitinib alone (6) and our study is the first case of FMF controlled by baricitinib alone. Both drugs target the Janus kinases (JAK) family of tyrosine kinases. One possible mechanism is inhibition of STAT activation, which would indirectly block the pathway in which IL-1 β plays a role.

Blau's syndrome is a rare autosomal dominant SAID. In 1985 Blau et al. described the presence of arthritis, iritis and skin lesions in 11 family members spanning four generations (7). The term Blau syndrome (OMIM# 186580) first proposed by Pastores was characterized by gradually developed camptodactyly(8). The syndrome results in significant joint militancy and morbidity if uncontrolled. It is a monogenic autosomal dominant disorder associated with at least 14 pathogenic variants located in the central NOD domain. These *NOD2* mutations are located in between the leucine-rich repeat region and the nucleotide binding domain. The high penetrant *NOD2* variants include R334W, R334Q, E383K, E383G, G464W, L469F, W490L, M513R, R587C, T605N, H496L, M513T, C495Y, and N670K (9). Heterozygous mutations in *NOD2* were discovered within exon 4, c.1000 C>T (p.Arg334Trp) of Case 2 and c.912C>T (p.Gly304Val) of Case 3. The mutations are likely to be disruptive, resulting in changes to protein structure or function. Loss of structure or function variants of *NOD2* are known to be pathogenic. The patient's uveitis started responding in the form of decreasing anterior chamber inflammation and iris nodules in case 2 and 3. And both cases had gained prominently alleviation on arthralgia and uveitis after initiating baricitinib administration.

More recently, *PLCG2* were linked to some clinical phenotypes including PLAID, APLAID, FCAS3 and CVID. The gene *was* located on the 16th chromosome (16q23.3) encodes phospholipase $\text{C}\gamma 2$ (*PLCG2*), a transmembrane signaling enzyme that catalyzes the production of second messenger molecules and propagates downstream signals in several hematopoietic cells (10).

FACS3 is an emerging entity and increasingly recognized as autoinflammatory disease characterized by cutaneous urticaria, erythema and pruritus in response to cold exposure, arthritis/distal extremity swelling due to the dysfunction of the inflammasome(10). It is one of the cryopyrin associated periodic syndromes caused by mutations in the *PLCG2* gene. Affected individuals may have additional immunological defects, including antibody deficiency, decreased number of B cells and increased susceptibility to infection (11). As for the therapy, glucocorticoids or cetirizine may be considered as the first-line treatment option and interleukin (IL)-1 blocker may be effective for refractory cases.

Current therapeutic approach with SAID patients is largely empirical and based on the clinical manifestations of the disease. The TNF-inhibitor has been proposed to be the first-line therapy for Blau syndrome in Chinese Han ethnicity people by Li et al. (12) and has also been used for colchicine-resistant FMF patients, especially with articular involvement(13). IL-1 blocker including rilonacept, canakinumab and anakinra are currently not available in Chinese market. Therefore, considering inaccessibility of adequate medical care during the pandemic of COVID-19, the practitioner administered alternative baricitinib monotherapy 4mg/day which has been widely applied in rheumatic disease including rheumatoid arthritis.

Since it is well known that the NOD2 variants in the nucleotide-binding domain region are involved in SAID syndrome(14) and Crohn's disease(15) (16). The Janus kinase (JAK) genetic variants are also associated with Crohn's disease and tofacitinib (JAK 1/3 inhibitor) are being evaluated for therapy targeting immune-mediated Crohn's disease(16). The defective gene in SAID is always mapped to 16th chromosome locus as shown in the previous 4 cases. In addition, the boosted whole exome displayed that these four patients manifested JAK 2 genotype of polymorphisms (*rs10758669*) C>A. The genotype has been proved to be related with JAK 2 activation in a Han Chinese population with Behcet's and Crohn's diseases(17). Those patients carrying the C risk allele displayed an increased JAK2 expression and NOD2 induced JAK2 phosphorylation compared with patients with the A allele(18).

Collectively, our aim is to describe a novel and alternative therapy of SAID syndrome with JAK inhibitors. Baricitinib is a small-molecule drug that targets the Janus kinases family of tyrosine kinases.

Furthermore, it has been used to treat RA, inflammatory bowel disease and alopecia areata (19). Baricitinib is specifically selective for JAK1/2 that allows blockage of the entire JAK2-STAT pathway, provoking important downregulation in the expression of some cytokines, such as IL-2, IL-6 and TNF- α , and subsequently exerting important immunosuppressive effects. To the best of our knowledge, this is the first report of SAID syndrome that has shown favorable response to baricitinib when biologics of anakinra, tocilizumab and TNF-inhibitors were unavailable during Covid-19 pandemic. Considering the JAK2 genotypic variant of *rs10758669* our observations also suggest a putative motivation to determine

the molecular mechanisms through which baricitinib induces remission in SAID patients. There were no serious adverse events warranting permanent discontinuation.

Conclusion

The study focuses on the autoinflammatory disease which is rare and a newly recognized group of immune disorders. The major clinical symptoms including fever, dermatitis, arthritis, gastrointestinal and sicca like symptoms that not specific and easily be misdiagnosed as “undifferentiated connective tissue disease”. This is the first report about SAID treated with JAK1/2 inhibitor. So, as a rheumatologist I really hope to share the successful experience with global rheumatologist, physicians and immunologists by your journal that owns most medical professional readers.

Abbreviations

SAID= Systemic autoinflammatory disease, FMF=Familial mediterranean feve,MEVF=Mediterranean fever gene, IL= interleukin, DIP=Distal interphalangeal, MCP=Metacarpophalangeal, NOD=Nucleotide-binding oligomerization domain, NLRP3= NLR family pyrin domain containing 3, JAK= Janus kinase, STAT=Signal transducer and activator of transcription, TNF- α = Tumour Necrosis Factor alpha, JIA=juvenile idiopathic arthritis, PLCG=Phospholipase C gamma,PLAID=PLCG2 associated antibody deficiency and immune dysregulation, APLAID, FCAS=Familial cold autoinflammatory syndrome, CVID= Common variable immunodeficiency

Declarations

- Ethical Approval and Consent to participate: It was approved by Tongji Hospital ethical committee and written informed consent forms were obtained from all four participants.
- Consent for publication: All authors have reviewed and approve this version of the manuscript.
- Competing interests: No
- Funding: From the Wuhan Scientific Funding for young investigators: 201271031432.
- Authors' contributions: SXH and RX wrote the main manuscript text. MY and XWH prepared figures and collected data. YKY designed the study. All authors reviewed the manuscript
- Acknowledgements: Special thanks to Dr. Lu yanjun for data processing
- Authors' information

1. SHAOXIAN HU, MD, Division of Rheumatology, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, Hubei, China

2. MEI YU, MD, Division of Stomatology, Wuhan Municipal Hospital of Traditional Chinese Medicine, Wuhan, Hubei, China
3. XIAOWEI HUANG, MD, Division of Digestive Medicine, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, Hubei, China
- 4 RUI XING, MD, Division of Rheumatology, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, Hubei, China
- 5.YIKAI YU, MD, Division of Rheumatology, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, Hubei, China

All the contribution of the work should be within Division of Rheumatology, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology

Declarations of interest: none

References

1. McDermott MF, Aksentijevich I, Galon J, McDermott EM, Ogunkolade BW, Centola M, et al. Germline mutations in the extracellular domains of the 55 kDa TNF receptor, TNFR1, define a family of dominantly inherited autoinflammatory syndromes. *Cell*. 1999;97(1):133-44.
2. Papa R, Rusmini M, Volpi S, Caorsi R, Picco P, Grossi A, et al. Next generation sequencing panel in undifferentiated autoinflammatory diseases identifies patients with colchicine-responder recurrent fevers. *Rheumatology (Oxford)*. 2020;59(2):344-60.
3. Neves JF, Doffinger R, Barcena-Morales G, Martins C, Papapietro O, Plagnol V, et al. Novel PLCG2 Mutation in a Patient With APLAID and Cutis Laxa. *Frontiers in immunology*. 2018;9:2863.
4. Kastner DL, Aksentijevich I, Goldbach-Mansky R. Autoinflammatory disease reloaded: a clinical perspective. *Cell*. 2010;140(6):784-90.
5. Bashardoust B. Familial Mediterranean fever; diagnosis, treatment, and complications. *J Nephropharmacol*. 2015;4(1):5-8.
6. Garcia-Robledo JE, Aragon CC, Nieto-Aristizabal I, Posso-Osorio I, Canas CA, Tobon GJ. Tofacitinib for familial Mediterranean fever: a new alternative therapy? *Rheumatology (Oxford)*. 2019;58(3):553-4.
7. Blau EB. Familial granulomatous arthritis, iritis, and rash. *J Pediatr*. 1985;107(5):689-93.
8. Pastores GM, Michels VV, Stickler GB, Su WP, Nelson AM, Bovenmyer DA. Autosomal dominant granulomatous arthritis, uveitis, skin rash, and synovial cysts. *J Pediatr*. 1990;117(3):403-8.
9. Parackova Z, Bloomfield M, Vrabцова P, Zentsova I, Klocperk A, Milota T, et al. Mutual alteration of NOD2-associated Blau syndrome and IFN γ R1 deficiency. *J Clin Immunol*. 2020;40(1):165-78.

10. Kutukculer N, Topyildiz E, Berdeli A, Guven Bilgin B, Aykut A, Durmaz A, et al. Four diseases, PLAID, APLAID, FCAS3 and CVID and one gene (PHOSPHOLIPASE C, GAMMA-2; PLCG2): Striking clinical phenotypic overlap and difference. *Clinical case reports*. 2021;9(4):2023-31.
11. Yao Q, Shen M, McDonald C, Lacbawan F, Moran R, Shen B. NOD2-associated autoinflammatory disease: a large cohort study. *Rheumatology (Oxford)*. 2015;54(10):1904-12.
12. Chen J, Luo Y, Zhao M, Wu D, Yang Y, Zhang W, et al. Effective treatment of TNFalpha inhibitors in Chinese patients with Blau syndrome. *Arthritis Res Ther*. 2019;21(1):236.
13. Ozen S, Demirkaya E, Erer B, Livneh A, Ben-Chetrit E, Giancane G, et al. EULAR recommendations for the management of familial Mediterranean fever. *Annals of the rheumatic diseases*. 2016;75(4):644-51.
14. Sfriso P, Caso F, Tognon S, Galozzi P, Gava A, Punzi L. Blau syndrome, clinical and genetic aspects. *Autoimmun Rev*. 2012;12(1):44-51.
15. Li Q, Lee CH, Peters LA, Mastropaolo LA, Thoeni C, Elkadri A, et al. Variants in TRIM22 That Affect NOD2 Signaling Are Associated With Very-Early-Onset Inflammatory Bowel Disease. *Gastroenterology*. 2016;150(5):1196-207.
16. Panes J, D'Haens GR, Higgins PDR, Mele L, Moscariello M, Chan G, et al. Long-term safety and tolerability of oral tofacitinib in patients with Crohn's disease: results from a phase 2, open-label, 48-week extension study. *Aliment Pharmacol Ther*. 2019;49(3):265-76.
17. Hu K, Hou S, Jiang Z, Kijlstra A, Yang P. JAK2 and STAT3 polymorphisms in a Han Chinese population with Behcet's disease. *Invest Ophthalmol Vis Sci*. 2012;53(1):538-41.
18. Prager M, Buttner J, Haas V, Baumgart DC, Sturm A, Zeitz M, et al. The JAK2 variant rs10758669 in Crohn's disease: altering the intestinal barrier as one mechanism of action. *Int J Colorectal Dis*. 2012;27(5):565-73.
19. Boland BS, Sandborn WJ, Chang JT. Update on Janus kinase antagonists in inflammatory bowel disease. *Gastroenterol Clin North Am*. 2014;43(3):603-17.

Tables

Talbe-1 Demographic features and clinical complications

Patients	1	2	3	4
Sex	Female	Male	Female	Female
Age at diagnosis (years)	18	17	17	23
Disease duration (years)	4	14	3	11
Family history	-	-	-	-
Clinical manifestations				
Polyarthrititis	+	+	+	+
Skin disease	+	+	+	+
Fever	+	-	-	+
Ocular	-	+	-	-
Sicca-like symptoms	-	-	-	-
GI symptoms	+	-	-	+
Laboratory finding				
WBC ^a (× 10 ⁹ / L)	5.21	6.53	8.70	3.47
ESR ^b (mm/h)	5	16	22	48
CRP ^c (mg/dL)	4.01	3.48	11.2	10.4
IL-1 β (pg/ ml)	27.8	78.0	125.5	170.2
IL-6 (pg/ml)	111.0	104.0	12.5	66.7
TNF- α (pg/ ml)	245.0	114.0	56.1	156.2
Total B lymphocyte % %CD3-CD19+	15.0	16.0	7.0	3.0
Cytotoxic T lymphocyte % %CD3+CD8+	33.00	27.00	48.00	24.00
Helper T lymphocyte % %CD3+CD4+	45.00	43.00	27.00	41.00
NK lymphocyte % %CD3-CD16+CD56	5.0	10.0	6.0	20.0
Genotyping	M680I	R334W	G304V	Y647S
rs10758669	AC	AC	CC	AC
Diagnosis	FMF	Blau	Blau	FACS3

^a WBC: White blood cells $4-10 \times 10^9 / L$, ^bESR:Erythrocyte sedimentation rate $0-20 mm/h$, ^c CRP c -reactive protein $0-10 mg/dl$. The level of plasma cytokines (Range: IL-1 β $5 pg/ml$, IL-6 $7 pg/ml$, TNF- α $8.1 pg/ml$). Analysis for ratio of peripheral lymphocytes. (Range: Total B lymphocyte: 5-18%, Helper T lymphocyte: 27-51%, Cytotoxic T lymphocyte: 15-44%, NK lymphocyte: 7-40%).

Table 2 The Tel Hashomer Diagnosis Criteria for familial Mediterranean fever

ClinicalCriteria	Comments
Major	
1	Recurrent febrile episodes with serositis (peritonitis, synovitis or pleuritis)
2	Amyloidosis of AA type without a predisposing disease
	Favorable response to regular colchicine treatment
3	
Minor	
1	Recurrent febrile episodes
2	Erysipelas-like erythema
3	FMF in a first-degree relative
Molecular criterion	MEVF

Figures

Figure 1

- a. Identification of the *MEFV* p.Met680Ile (c.2040 G>T) mutation in case 1 patient
- b Ichthyosis plaques on the cheeks in case 2 patient
- c The anterior segment picture of the eyes showed granulomatous uveitis in case 2 patient
- d. Identification of the *NOD2* p.Arg334Trp (c.1000 C>T) mutation in case 2 patient
- e Camptodactyly in case 3 patient
- f T1 axial (left) ,fat saturation T2 coronal (middle) and fat saturation T2 coronal (right) images demonstrating tissue edema in case 3 patient.
- g. Identification of the *NOD2* p.Gly304Val (c.912 C>T) mutation in case 3 patient
- h. Erythematous plaques on left neck and shoulders in case 4 patient
- i. Identification of the *PLCG2* p.Tyr647Ser (c.1940 A>C) mutation in case 4 patient