ISG15 deficiency underlie monogenic lupus with inflammatory myositis

Sulaiman M Al-Mayouf[1,2], Lujayn Akbar[1]
Pediatric Rheumatology, Department of Pediatrics[1],
King Faisal Specialist Hospital & Research Center, College of Medicine, Alfaisal University[2] .

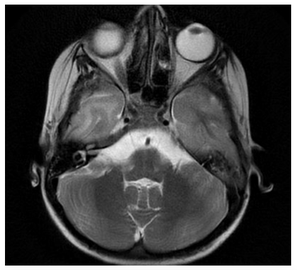
Background

Rare SLE subtypes characterized by early onset, secondary to a single gene mutation are defined as monogenic lupus. complement deficiencies and interferonopathies are among the leading causes of monogenic lupus.

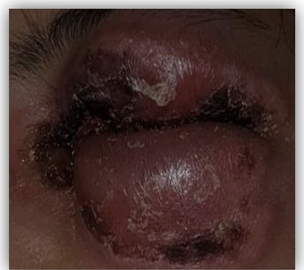
Interferon-stimulated gene 15 (ISG15) deficiency is an inherited disorder under the umbrella of interferonopathies, manifested with immunological, neurological and dermatological features.

Clinical Case

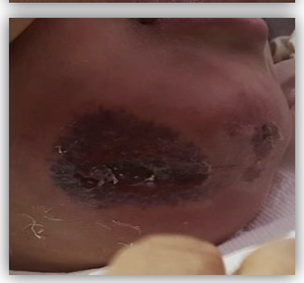
A 14-year-old girl, presented at the age of 7 years with generalized seizures and respiratory failure.



Investigations revealed thrombocytopenia.
Brain MRI: diffuse T2 hyperintensities in the temporal lobes.
Subsequently, she suffered R-sided hemiparesis, autistic features, and neuropsychiatric regression.

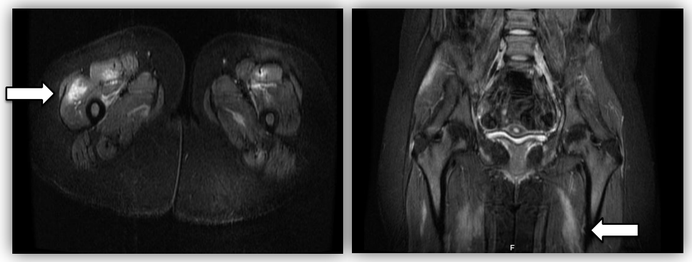


One year later, she experienced recurrent fever, oral ulcers, facial rash, and periorbital swelling,.
ANA 1:160 with positive dsDNA, low C3 level, normal C4, and normal C1q level.



Skin biopsy: focal interface dermatitis with necrotic keratinocyte and scattered dermal veno-occlusive disease.
She had silvery- gray hair. Hair shaft microscopy: hypopigmentation and large pigment clumps.

She lost follow-up and presented at the age of 14-years with fever, oral ulcers, fatigability, weight loss, arthritis, and proximal lower limb muscle weakness.
MRI of the the pelvis and thighs showed bilateral asymmetric active myositis. Also; she had positive antibodies to Mi-2.



Other relevant laboratory findings are summarized in the Table.
She was diagnosed with SLE and myositis.

Trio-WES identified a homozygous splicing site ISG15 mutation (c.4-1G>A), parents were heterozygous. In addition to pathogenic homozygous variants in MLPH gene.

The diagnosis of ISG15 deficiency with monogenic lupus was established.
She was treated aggressively with methylprednisolone, hydroxychloroquine, MMF, belimumab, and IVIG with favorable response.

Conclusion

Our finding expanded the phenotypic spectrum of ISG15 deficiency to SLE manifestations and inflammatory myositis, highlighting the phenotypic heterogeneity and overlap between autoinflammatory and autoimmune diseases. Recognizing patients with unusual phenotype should be genetically screened for pathogenic variants.

	Initial presentation	Lupus expression	Last follow-up
WBC (3.9-11 10^9/L)	5.10	4.5	6.05
Hemoglobin (110-16 g/L)	91	91	127
Platelets (155-435 10^9/L)	Low	308	286
ESR (mm/Hr)	35	77	19
C3 (0.9-1.8 g/L)	Low	0.60	0.90
C4 (0.1 – 0.4 g/L)	Normal	0.08	0.19
ANA (< 1:40)	1:160	1:1280	1:320
Anti-dsDNA	78.9 (<20 IU/mL)	770 (0-200 IU/mL)	386 (0-200 IU/mL)
Anti-Sm (0-19.9 units)	Negative	3.3	1.6
CK (24-195 U/L)	-	665	84
AST (10-45 U/L)	27.9	62.7	26
ALT (10-45 U/L)	18.8	30	21
LDH (120-300 U/L)	-	544	323

Email: almayoufsulaiman@yahoo.com