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SHORT COMMUNICATION

Interferonopathies at the crossroads of monogenic lupus and autoinflammation: A case study

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Abstract

Monogenic lupus is a highly complex condition with marked variability, resulting from diverse immune system etiopathogenesis linked to various pathogenic genetic variants. There is substantial overlap with newly described systemic autoinflammatory disorders. We present two cases of monogenic lupus and highlight the intersection between monogenic lupus and autoinflammatory disorders. This report emphasizes the concept of monogenic interferonopathies as an umbrella term for various conditions arising from genetic aberrations in type I interferon (IFN-I) signaling, which are associated with significant IFN-I activation.

Keywords: Monogenic lupus; Systemic lupus erythematosus; Type I interferon; Interferonopathies

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1. Introduction

Systemic sterile inflammatory disorders can be broadly categorized using the semantic immunological concepts of autoimmunity and autoinflammation, each with distinct etiopathogenic mechanisms. Autoimmune disorders primarily involve defects in the adaptive immune system, characterized by the presence of autoantibodies and autoreactive T or B lymphocytes. In contrast, classic autoinflammatory disorders are linked to aberrations in innate immunity, occurring in the absence of autoantibodies and autoreactive lymphocytes, and typically involve the secretion of a single cytokine, often due to genetic mutations.[1-3] Recent advancements in molecular genetics approaches and immunological diagnostics have revealed a variety of innate immune pathways involved in autoinflammatory disorders, including type I interferon (IFN-I), which plays a crucial role in the pathogenesis of several such conditions. This has expanded the spectrum of autoinflammatory disorders, with interferonopathies recently recognized as a subset.[4-7] Notably, while autoinflammatory disorders may arise from a single gene localized in the innate immune system, there is considerable overlap in the pathogenic mechanisms involving the adaptive immune system. This overlap leads to common clinical features observed in both monogenic and polygenic disorders, including diverse patterns of multiorgan involvement and variable clinical presentations.[1,3] Systemic lupus erythematosus (SLE), a prototypical autoimmune disease, is characterized by the loss of self-tolerance, excessive production of pathogenic autoantibodies, and dysregulated

immune complex deposition. Several immune phenomena, such as defective regulatory T cells, impaired lymphocyte homeostasis, and defects in the clearance of apoptotic cells and immune complexes, may contribute to these features.[8,9] Despite remarkable advancements in understanding the etiopathogenesis of SLE, its precise etiology remains elusive. SLE is widely accepted as a polygenic, multifactorial disease influenced by a complex interplay of genetic, epigenetic, environmental, and hormonal factors.[10,11] Notably, a subset of patients exhibits lupus features linked to a single genetic mutation, classifying them as having monogenic lupus.[12-15] Interestingly, the genetic mutations responsible for these pathogenic pathways lead to a robust production of IFN-I, which drives monogenic lupus pathogenesis by promoting inflammatory reactions, plasmacytoid dendritic cell maturation, autoreactive T and B cell activation, and tissue damage, similar to the phenomena proposed for polygenic or multifactorial lupus.[16]

In this work, we explore the intersection between monogenic lupus and systemic autoinflammatory disorders (SAIDs) by reporting two cases of monogenic lupus that were classified as SAIDs.

2. Patients and methods

This retrospective report analyzed two monogenic lupus patients carrying pathogenic genetic mutations. Medical records were reviewed to collect demographic and clinical data, laboratory results, genetic findings, imaging and histopathology results, and therapeutic responses.

This study adheres to the ethical principles outlined in the Declaration of Helsinki (2000); the Research Advisory Council guidelines of King Faisal Specialist Hospital and Research Center, Riyadh; and the Saudi Arabian legislation. This work was conducted as part of a previously approved study (study number 2221105). All clinical and laboratory assessments were performed as part of the standard medical care. Informed consent for genetic testing was obtained from the parents during blood extraction, as part of patient care. All collected data were examined under confidentiality practices, ensuring no personal information was disclosed. Verbal consent was obtained from each patient's parents for publication of their data and/or images.

3. Results

The first case involves a 12-year-old boy who initially presented at 3 years of age with intermittent fever and painful polyarthritis affecting the small joints of hands, elbows, knees, and ankles. In addition, he exhibited multiple finger contractures (Figure 1). Other systemic assessments were unremarkable. Laboratory findings

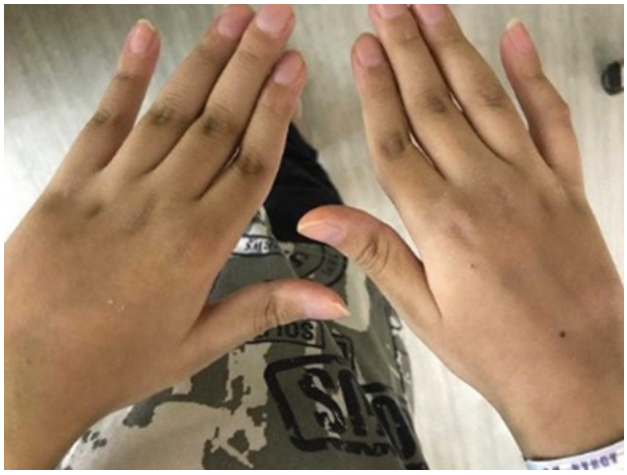

Figure 1. Multiple finger contractures

included a positive direct Coombs test, pancytopenia, elevated erythrocyte sedimentation rate, positive antinuclear antibody (ANA), double-stranded DNA (dsDNA) antibodies, and anti-cardiolipin antibodies (IgG and IgM), along with a low complement (C_3) level. Bilateral hand X-rays showed soft tissue swelling with non-erosive deformities of the fifth fingers. Initial treatment consisted of systemic corticosteroids, methotrexate, and an anti-tumor necrosis factor (TNF) agent (adalimumab) for 3 months. Due to poor response, the anti-TNF agent was switched to rituximab, which led to partial improvement, though frequent relapses were still observed. Follow-up assessments revealed progressive headache and bilateral papilledema. Further laboratory assessment revealed a negative neuromyelitis optica antibody test. Brain magnetic resonance imaging (MRI) showed multiple scattered patchy hyperintense lesions in the bilateral cerebral white matter, with unremarkable intracranial magnetic resonance angiography and magnetic resonance venography (Figure 2). Whole exome sequencing identified a homozygous c.902C>T (p.S301P) variant in the *DNase II* gene, leading to the diagnosis of monogenic lupus due to DNase II deficiency.

The second case has been previously reported.[17] In brief, the patient was diagnosed with monogenic lupus, initially presenting with constitutional symptoms, oral ulceration, polyarthritis, and myositis involving pelvic and thigh muscles, confirmed by MRI findings. Laboratory results showed elevated muscle enzymes, high acute-phase reactants, low complement (C_3 and C_4) levels, and elevated ANA and dsDNA antibodies. Whole exome sequencing identified a homozygous splicing site, *ISG15* variant (c.4-1G>A). Table 1 presents the pathogenic genetic variants identified in our patients with monogenic lupus.

Table 1. Pathogenic genetic variants of our patients with monogenic lupus

Patient	Gene	Mechanism	Mutation	Zygosity	Inheritance
Patient 1	*DNase II*	Loss of function	NM_001375:c. 902C>T (p.S301P)	Homozygous	Recessive
Patient 2	*ISG15*	Loss of function	NM_005101: c. 4-1G>A	Homozygous	Recessive

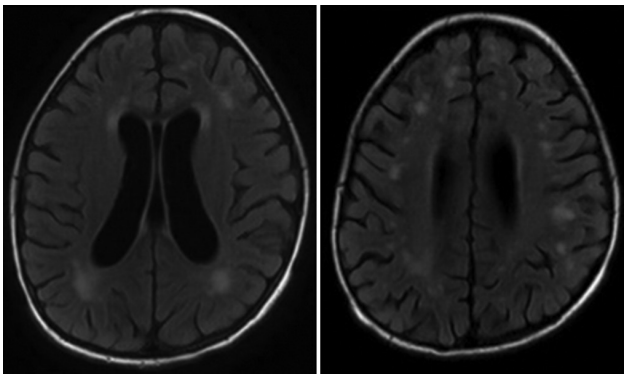

Figure 2. Brain magnetic resonance imaging showing multiple scattered hyperintense lesions in the bilateral cerebral white matter

Both patients were treated with systemic corticosteroids, starting with methylprednisolone pulse therapy for 3 days, followed by tapered maintenance dosages (1 mg/kg/day), hydroxychloroquine (200 mg daily), mycophenolate mofetil (500 mg twice daily), and belimumab (10 mg/kg/dose) infusion. Notably, they were eventually able to discontinue corticosteroid use. Table 2 outlines the clinical and laboratory features, as well as the treatment regimens, for these two patients with monogenic lupus. Unfortunately, the interferon signature analysis was not performed for either patient due to its unavailability at our institution.

4. Discussion

We present two patients who fulfilled the recently validated EULAR/ACR 2019 classification criteria for monogenic lupus.[15] Monogenic lupus is a complex construct characterized by a wide range of phenotypes and a paradoxical combination of immune dysregulation and autoimmunity, caused by various pathogenic mechanisms linked to pathogenic genetic variants.[18] At present, about 35 genes have been identified as predisposing to monogenic lupus.[13,18-20] Recent studies have identified that the second most prevalent cause of monogenic lupus involves variants in genes related to IFN-I signaling, which lead to significant IFN-I hyperactivation.[7,21,22] In addition, many newly identified SAIDs are primarily driven by various innate immune pathways beyond the interleukin (IL) family (*e.g.*, IL-1 and IL-18), or inflammasome-mediated disorders, and are characterized by elevated IFN-I production.[7] The phenotypic features of these recently described SAIDs, including actinopathies, nuclear factor kappa B-mediated conditions, and interferonopathies, often deviate from the typical features of the classic SAIDs, particularly inflammasomopathies. Patients with these conditions are more likely to experience a progressive disease course rather than periodic attacks, and they often present with autoimmune phenomena such as the presence of autoantibodies, further demonstrating the inseparable division between innate and adaptive immunity.[6,7,22,23] Monogenic lupus variants affecting the interferonopathy pathway are often associated with autoinflammatory clinical and laboratory features, whereas variants involving B-cell and T-cell dysfunction tend to present with autoimmune characteristics (Figure 3).

Our first patient, with a loss-of-function variant in the *DNase II* gene mirrors cases described by Rodero *et al.*,[24] who identified a type I interferonopathy in humans caused by DNase II deficiency. This deficiency impairs the clearance of apoptotic, necrotic, and neutrophil extracellular traps, which are primary sources of self-dsDNA. The accumulation of self-dsDNA can stimulate autoreactive B cells to produce autoantibodies in conjunction with autoreactive T cells. The resulting dsDNA immune complexes trigger phagocytes and plasmacytoid dendritic cells to produce substantial amounts of IFN-I through various intracellular DNA sensors.[24,25]

The second patient was confirmed to have a loss-of-function variant in *ISG15*. The deficiency in *ISG15* leads to unstable levels of ubiquitin-specific peptidase 18, a negative regulator of IFN-I signaling. Consequently, the absence of ISG15 results in persistent expression of interferon-stimulated genes, presenting with severe inflammatory phenotypes that include autoimmune and autoinflammatory features.[17,26]

In light of the significant role of IFN-I in the pathogenesis of monogenic lupus, it is important to acknowledge the complex immunological networks that further amplify inflammatory responses. Recent studies suggest a critical interaction between IFN-I signaling, Th17 cells, and soluble HLA-G (sHLA-G), which together contribute to immune dysregulation in chronic immune-mediated diseases. Th17 cells, known for their role in mucosal immunity and inflammation, are influenced by the IFN-I axis, with evidence indicating enhanced Th17

Table 2. Clinical and laboratory features and treatment regimens for patients with monogenic lupus

	Patient 1	Patient 2
Gender	Male	Female
Age at onset	3 years	7 years
Age at diagnosis	12 years	12 years
Clinical features		
Constitiutional	Fever, fatigability, weight loss	Fever, fatigability, weight loss
Mucocutaneous	No	Facial rash, oral ulcers, periorbital swelling
Musculoskeletal	Painful polyarthritis	Polyarthritis, proximal muscle weakness
Neuropsychiatric	Headache, papilledema	Seizure, behavioral, learning disability
Renal	No	No
Lung	No	No
Cardiac	No	No
Gastrointestinal	No	No
Recurrent infection	No	No
Laboratory features		
ANA	1:1280	1:1280
dsDNA	1294	770
Hematologic	Leukopenia, DC positive anemia	Anemia
Acute-phase reactants	High ESR, CRP	High ESR, CRP
Serum immunoglobluins	High	Normal
Brain imaging (MRI)	Multiple scattered hyperintense lesions in the bilateral cerebral white matter	Bilateral diffuse T2 hyperintensities in the temporal lobes
Treatment	HCQ, MMF, belimumab	HCQ, MMF, belimumab
Present status	Stable general condition, persistent deforming arthropathy	Stable general condition, behavioral, and learning disability

Abbreviations: ANA: Antinuclear antibody; CRP: C-reactive protein; DC: D-Coombs; dsDNA: double-stranded DNA; ESR: Erythrocyte sedimentation rate; HCQ: Hydroxychloroquine; MMF: Mycophenolate mofetil; MRI: Magnetic resonance imaging.

polarization under interferon-driven environments. Moreover, sHLA-G, an immunomodulatory molecule, has been reported to impact both innate and adaptive immunity, potentially modulating the balance between regulatory and pro-inflammatory responses. These interactions are thought to drive persistent inflammation and autoimmunity, as highlighted in recent studies by Murdaca *et al.*[27] and Contini *et al.*[28] Incorporating the interplay between IFN-I, Th17 cells, and sHLA-G into the understanding of monogenic lupus may help clarify the diverse and overlapping immunopathogenic features observed in these cases.

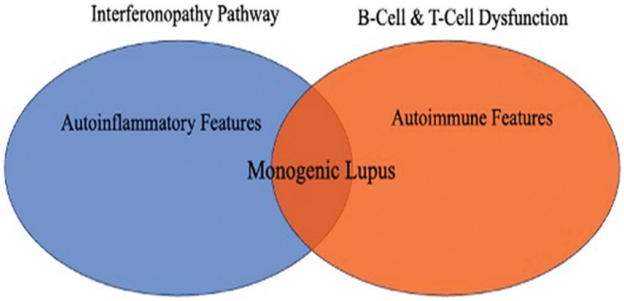

Figure 3. The distinction between monogenic lupus variants associated with interferonopathy (autoinflammatory features) and those involving B-cell/T-cell dysfunction (autoimmune features)

At present, there are no approved medications specifically for patients with monogenic lupus or interferonopathies. However, available medications, including biologic agents, are used off-label. Our patients were successfully treated with corticosteroids, hydroxychloroquine, mycophenolate mofetil, and belimumab. Emerging treatment modalities, such as Janus Kinase inhibitors (*e.g.*, tofacitinib, baricitinib, or ruxolitinib), interferon receptor blockade (*e.g.*, anifrolumab), or agents targeting free phases of type I interferons (*e.g.*, sifalimumab or rontalizumab), show promise for treating interferonopathies.[7] Notably, the recent approval of anifrolumab, in addition to belimumab, has expanded treatment options for lupus in general.[29-31]

This report highlights the growing recognition of shared immunopathogenic pathways between monogenic lupus and autoinflammatory disorders, particularly in the context of type I interferon-mediated disease. Monogenic lupus exhibits significant variability due to diverse immune system etiopathogenesis. The interferon pathway, which connects autoimmunity and autoinflammation by linking innate and adaptive immune responses, is associated with a range of genetic variants responsible for monogenic lupus. However, considering monogenic lupus under autoinflammatory classification may not be ideal, given lupus's historical classification as an autoimmune disease. Therefore, we propose adopting the concept of monogenic interferonopathies as a stand-alone category. This category would encompass a broad spectrum of conditions, including monogenic autoinflammatory, monogenic lupus, as they bridge autoimmune and autoinflammatory disorders. However, a consensus is required to formulate the monogenic interferonopathies taxonomy and nomenclature.

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Conflict of interest

The authors declare that they have no competing interests.

Author contributions

Conceptualization: All authors
Investigation: All authors
Methodology: Sulaiman M. Al-Mayouf
Writing – original draft: Sulaiman M. Al-Mayouf
Writing – review & editing: All authors

Ethics approval and consent to participate

This study adheres to the ethical principles outlined in the Declaration of Helsinki (2000); the Research Advisory Council guidelines of King Faisal Specialist Hospital and Research Center, Riyadh; and the Saudi Arabian legislation. This work was conducted as part of a previously approved study (study number 2221105). All clinical and laboratory assessments were performed as part of the standard medical care. Informed consent for genetic testing was obtained from the parents during blood extraction, as part of patient care. All collected data were examined under confidentiality practices, ensuring no personal information was disclosed.

Consent for publication

Verbal consent was obtained from each patient's parents for publication of their data and/or images.

Availability of data

Data are available from the corresponding author upon reasonable request.

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