A Familial STING: A Father and Daughter Journey to SAVI Diagnosis

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STING-associated vasculopathy with onset in infancy (SAVI) is a rare monogenic type I interferonopathy that may present with heterogeneous clinical manifestations and mimic common inflammatory disorders of childhood. We report the first familial case of SAVI in Israel, affecting a father and daughter carrying an identical pathogenic gain-of-function TMEM173 variant. The daughter initially presented with features fulfilling criteria for rheumatoid factor-positive juvenile idiopathic arthritis (JIA), later developing growth failure and progressive interstitial lung disease. In contrast, the father developed adolescent-onset inflammatory arthritis, subsequently lung disease, and a severe infectious neurological complication during treatment. This case highlights marked intrafamilial phenotypic variability, the diagnostic challenges posed by atypical inflammatory arthritis and the importance of genetic testing in treatment-refractory or systemic disease. Our findings underscore both the benefits and limitations of JAK inhibition in SAVI, particularly with respect to pulmonary disease and growth outcomes.

JIA is the most common chronic rheumatologic and one of the most common chronic diseases of childhood. Its diagnosis requires the exclusion of other causes of arthritis. Advances in genetic testing have identified monogenic autoinflammatory disorders that may mimic the condition, particularly in atypical or treatment-refractory cases.

Autoinflammatory diseases represent a rapidly expanding group of rare disorders caused by dysregulation of the innate immune system, leading to recurrent or persistent systemic inflammation. Timely and accurate diagnosis of the specific disorder identifies targets for therapy and is critical for preventing severe complications and reducing mortality. Our case highlights the phenotypic overlap of JIA with SAVI and demonstrates the importance of genetic evaluation in familial or atypical inflammatory arthritis, especially with lung or systemic disease.

PATIENT DESCRIPTION

A 2-year-old girl, youngest of four, presented with a 4-month history of intermittent morning irritability and joint stiffness, followed by a gait disturbance without clear limping. Her medical history included infancy pneumonia and asthma treated with inhaled corticosteroids and montelukast. Developmental milestones were appropriate for her age. Family history included paternal psoriatic arthritis treated during adolescence by the same pediatric rheumatologist with intra-articular corticosteroid injections and hydroxychloroquine. Her mother and siblings were healthy.

Physical examination revealed an underweight child with hesitant gait and in-toeing, but no apparent arthritis or other abnormalities. White blood counts and biochemistry were normal. ESR, C-reactive protein, gamma globulins, and rheumatoid factor (RF) were elevated. Antinuclear antibodies were positive at least once. Two months later, signs of wrist arthritis emerged, confirmed by magnetic resonance imaging. Following appearance of bilateral ankle arthritis and polyarthralgia, a diagnosis of polyarticular RF positive JIA was made and methotrexate therapy was initiated. Arthritis rapidly improved and inflammatory markers decreased but poor weight gain and a decreased appetite persisted. Evaluation at the gastroenterology clinic attributed these symptoms

to methotrexate side effects and familial tendency. Ophthalmologic screening revealed no uveitis. At age 4 years, after achieving complete clinical remission for over one year, methotrexate was discontinued. Subsequent follow-up was remarkable for episodic musculoskeletal pain without arthritis, persistent cough, and anorexia.

An extensive pulmonary and immunologic evaluation was initially unremarkable. At age 5 years, following pneumonia, a chest computed tomography (CT) scan demonstrated mediastinal lymphadenopathy, pulmonary fibrosis, and microbullae consistent with interstitial lung disease (ILD). Concurrently, the mother reported a paternal history of chronic respiratory difficulties.

The constellation of familial arthritis, atypical RF-positive JIA, growth failure, lung disease with characteristic CT findings, and elevated inflammatory markers raised suspicion of an underlying genetic autoinflammatory syndrome, specifically SAVI. The diagnosis was confirmed via whole-exome sequencing, which identified a pathogenic heterozygous gain-of-function variant in STING1 (TMEM173): c.842G>A (p.Arg281Gln).

After failing multiple therapies, the father initially improved on the JAK inhibitor tofacitinib and systemic corticosteroids but subsequently developed progressive neurological deterioration. Cerebrospinal fluid polymerase chain reaction detection of JC virus confirmed a diagnosis of progressive multifocal leukoencephalopathy (PML), representing the first documented case of JAK inhibitor-associated PML in Israel [2]. Partial neurological recovery was achieved after drug discontinuation and intensive rehabilitation.

Following SAVI diagnosis, ruxolitinib (a JAK1/2 inhibitor) therapy was recommended. Although the family was initially hesitant due to the father's medical complications, they agreed to treatment due to clinical deterioration. Constitutional and musculoskeletal symptoms and inflammatory markers improved; however, growth remained suboptimal, and lung function and imaging failed to improve. Due to this partial response, switching to alternative interferon-targeted therapy was considered.

COMMENT

The same pathogenic TMEM173 gain-of-function variant resulted in marked intrafamilial phenotypic variability, with adolescent-onset inflammatory arthritis and interstitial lung disease in the father and early onset polyarthritis, growth failure, and progressive interstitial lung disease in the daughter. Such divergence despite identical mutations suggested contributions from genetic modifiers, environmental factors, or age-dependent immunological context [3] and illustrated the diagnostic challenge of distinguishing SAVI from juvenile idiopathic arthritis when musculoskeletal and systemic features overlap.

The patient initially fulfilled ILAR criteria for RF-positive JIA and showed clinical response to methotrexate; however, subsequent systemic manifestations prompted reconsideration of the diagnosis.

SAVI is a type I interferonopathy due to TMEM173 gain-of-function variants. Constitutive activation of the STING pathway, upregulation of type I interferon signaling and widespread immune dysregulation causes chronic systemic inflammation and multiorgan involvement. Recent reviews published in 2023 emphasize early recognition of monogenic interferonopathies that may mimic autoimmune disease and highlight the persistent limitations of current targeted therapies in SAVI, particularly with respect to pulmonary outcomes [4,5]. Most cases are autosomal dominant. European League Against Rheumatism/American College of Rheumatology (EULAR/ACR) frameworks emphasize early recognition of interferonopathies that may mimic autoimmune disease. SAVI symptoms include early onset cutaneous vasculopathy, as well as systemic inflammation, including fever, fatigue, and elevated inflammatory markers [1]. Many patients also develop interstitial lung disease (ILD), which can be progressive and life-threatening, as well as polyarticular arthritis, which reflects the involvement of both pulmonary and musculoskeletal systems [1,4]. Pulmonary disease is a major determinant of morbidity and mortality in SAVI. The chest CT findings of mediastinal lymphadenopathy, fibrosis, and early bullous changes aligned with the typical radiographic spectrum described in affected children. Additional manifestations may include growth impairment, recurrent infections [4], and vascular or renal complications.

The nutritional burden associated with SAVI is a significant complication, driven by chronic systemic inflammation and elevated metabolic demands [4]. In our patient, poor growth persisted despite improved inflammation, suggesting an intrinsic disease-related contribution.

Mechanistically, growth impairment in SAVI reflects a combination of chronic interferon-driven catabolism, elevated metabolic expenditure associated with progressive intersti-

tial lung disease, cytokine-mediated appetite suppression particularly along the IL-6 axis, and potential effects of sustained systemic inflammation on the GH–IGF-1 axis. These mechanisms are consistent with growth trajectories observed in other interferonopathies [4].

Another factor contributing to delayed diagnosis was absence of cutaneous manifestations, classically a hallmark of SAVI. Cutaneous vasculopathy, most often acral, represents one of the earliest and most recognizable features of the disease. Typical dermatologic findings include cold sensitive violaceous skin lesions on fingers and nose, progressing to livedo reticularis, chilblains, telangiectasias, ulcerations, and digital gangrene. However, up to 10% have no skin manifestations [4]. Absence of characteristic acral vasculopathy may obscure the clinical picture and lead to erroneous diagnoses.

Positive RF antibodies deserve particular attention. These autoantibodies are classically associated with rheumatoid arthritis and RF-positive polyarticular JIA, reported in several interferonopathies including SAVI. This distinction is clinically important. In the context of interferonopathies, RF positivity often reflects non-specific B-cell activation rather than true autoimmune pathogenesis and therefore should not dissuade clinicians from considering monogenic autoinflammatory diseases when systemic or atypical features are present [1].

JAK inhibitors altered the management of interferonopathies by attenuating interferon-driven inflammation, but pulmonary outcomes are inconsistent [4,5]. JAK blockade may reduce systemic inflammation but often fails to halt ILD progression. Partial response to ruxolitinib mirrors outcomes in multicenter cohorts that show that ruxolitinib, baricitinib, and tofacitinib can attenuate interferon-driven inflammation in SAVI [5] but not always ILD. Ongoing trials are exploring more selective inhibitors of the interferon pathway.

This research aligns with the EULAR/ACR framework emphasizing individualized therapy and comprehensive monitoring and highlights the limitations of current targeted treatments, phenotypic variability despite identical mutations, and the impact of nutritional compromise.

CONCLUSIONS

The differential diagnosis of pediatric inflammatory arthritis continues to expand with the recognition of monogenic autoinflammatory diseases. This case underscores the importance of genetic testing in pediatric rheumatology and highlights both the therapeutic potential and limitations of JAK inhibition in SAVI, particularly regarding pulmonary outcomes and growth.

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Capsule

Continuous or fixed-duration maintenance therapy in multiple myeloma

In this phase 3 randomized clinical trial, **Kumar** and colleagues compared continuous maintenance therapy with a fixed-duration maintenance strategy in patients with newly diagnosed multiple myeloma who had achieved disease control after initial treatment. The study demonstrated that continuous maintenance therapy significantly prolonged progression-free survival compared with fixed-duration maintenance. Patients receiving ongoing therapy maintained deeper and more durable responses with higher rates of sustained minimal residual disease (MRD) negativity. Although continuous treatment was associated with increased cumulative adverse events, including hematologic toxicity and infections, the safety profile remained manageable, and treatment discontinuation rates were acceptable. Overall survival data were still immature at the time of publication.

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