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Failure to thrive, interstitial lung disease, and progressive digital necrosis with onset in infancy

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CASE SUMMARY

History

An 18-year-old Turkish male was referred to the National Institutes of Health (NIH) for evaluation of failure to thrive, interstitial lung disease, and progressive digital necrosis of 16 years duration. The patient was born after an uneventful pregnancy and was first hospitalized at 6 months of age for failure to thrive, malnutrition, and recurrent cough. At 18 months of age he developed chronic fluid discharge from perforation of the left tympanic membrane and was noted to have violaceous and telangiectatic plaques over the malar area. At 24 months of age he developed swelling of the left fourth finger that quickly progressed to necrosis and autoamputation of the distal phalange. Further tissue destruction had occurred annually during the winter months and progressed to involve the ears, toes, nasal septum, and knees. The patient also reported easy fatigueability, chronic joint pain of the knees, ankles, elbows, and proximal interphalangeal joints, and chronic myalgias of the

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Note: Dr. Chia evaluated this patient during an elective rotation at the NIH.

Editor's note: Dr. Goldbach-Mansky at the NIH in Bethesda, Maryland is currently studying patients with autoinflammatory syndromes. Clinicians can refer interested patients to the NIH Patient Recruitment and Referral office at 800-411-1222 or by e-mail to prpl@mail.cc.nih.gov.

lower extremities. His previous therapies included intravenous methylprednisolone, iloprost, pentoxifylline, acetylsalicylic acid, stanozolol, azathioprine, and nifedipine without benefit.

The patient had a fraternal twin bother in good health and there was no family history of a similar disorder.

Physical examination

Physical examination revealed a cachectic individual with violaceous to tan-colored atrophic papules and plaques on the nose and bilateral malar cheeks. There was partial loss of both helices with atrophic scarring (Fig 1). Violaceous discoloration was noted over the knees with overlying crusts and associated atrophy. There was thick, hyperkeratotic scale overlying the lateral aspects of the feet extending to the heels. The distal extremities were remarkable for amputation of several digits on the hands and feet with overlying scale, atrophy, and a violaceous hue (Fig 2).

Histopathology

Histopathologic examination of skin biopsy specimens from both knees revealed hyperkeratosis, mild epidermal atrophy, and vacuolar change in the basal cell layer. Dilated vessels with large collections of erythrocytes were remarkable in the papillary dermis. Fibrin thrombi were seen within small vessels of the dermis and stained positive for fibrinogen and C3. A mild perivascular lymphocytic infiltrate with rare neutrophils and mild karyorrhexis was observed in the dermis (Fig 3).

Significant diagnostic studies

Laboratory investigations were notable for a white blood cell count of 8.53 K/ μ L (normal, 4.23-9.07 K/ μ L) with an absolute neutrophil count of 6.32 K/ μ L (normal, 1.78-5.38 K/ μ L) and 3.3% monocytes (normal, 5.3-12.2%); a hemoglobin level of 11.8 g/dL (normal, 13.7-17.5 g/dL); and a platelet count of 526 K/ μ L (normal, 161-347 K/ μ L). Autoimmune workup revealed an elevated erythrocyte sedimentation rate (ESR) of 89 mm/hr, with a positive anti-nuclear antibody (1.4EU, normal < 1 EU), anti-dsDNA antibody and lupus anticoagulant, weakly positive anti-proteinase-3 antibody, and negative anti-myeloperoxidase antibody and anti-cardiolipin antibody (IgG, IgM). An elevated immunoglobulin E (IgE) level of 283 mg/dL (normal, < 90.0 mg/dL) and an IgG level of 4747 mg/dL (normal, 700-1600 mg/dL) were noted, with normal IgA and IgM. Computed tomography (CT) of the chest showed diffuse hyperinflation, ground-glass opacity, diffuse cystic changes in a subpleural and anterior lung distribution, as well as enlarged supraclavicular and axillary nodes. Magnetic resonance imaging showed bone resorption of affected distal phalanges. Mutation analysis revealed an N154S mutation in the *TMEM173* gene.

DIAGNOSIS

Stimulator of interferon genes (STING)-associated vasculopathy with onset in infancy (SAVI) with associated interstitial lung disease (OMIM #615934).

FOLLOW-UP

The patient was enrolled in an NIH study of the JAK inhibitor baricitinib for the treatment of autoimmune inflammatory diseases (ClinicalTrials.gov # NCT01724580) and since starting treatment no new lesions have developed.

DISCUSSION

SAVI is a type I interferonopathy syndrome, that presents with neonatal-onset systemic inflammation, severe cutaneous vasculopathy, and interstitial lung disease and was first described in 2014.¹ To date, there have been 11 published cases (Table 1) with 4 identified mutations in the *TMEM173* gene (p.V147L, p.V147M, p.N154S, p.V155M).¹⁻³ Cutaneous manifestations typically begin between birth and 6 months of age and present as erythematous- purpuric patches and plaques on cold-sensitive areas including the cheeks, nasal tip, ears, and acral sites. Prominent erythema involving the central cheeks with telangiectasia is characteristic, but pustular lesions, reticulate erythema of the limbs and digital edema may also occur. Over time, cutaneous lesions progress to painful ulcerations with eschar formation; sequelae include nasal and ear tissue loss with nasal perforation, nail destructions and digital gangrene necessitating surgical amputation. Disease flares often occur during winter months. The majority of patients also develop interstitial lung disease that may first present as tachypnea. Invariably, patients show signs and symptoms of systemic inflammation including elevated acute phase reactants, anemia of chronic disease, intermittent fevers, and failure to thrive. To date, immunosuppressive medications have been of little benefit.

STING is a key adaptor protein in the type 1 interferon (IFN) response to synthetic and viral double-stranded DNA (dsDNA).^{1, 4} Immunostimulatory dsDNA is first sensed in the cytosol by cyclic guanosine monophosphate-adenosine monophosphate (cGAMP) synthase (cGAS), producing the second messenger cGAMP, which is sensed by STING to induce interferon gene expression via the TANK-binding kinase 1 (TBK1) and transcription factor interferon receptor factor 3 (IRF-3).⁴ The gene encoding STING, *TMEM173*, is ubiquitously expressed at high levels in natural killer and T cells, endothelial cells, alveolar pneumocytes and macrophages, bronchial epithelium, and myeloid cells.^{1,2,5} In SAVI, missense mutations in *TMEM173* cause constitutive activation of STING resulting in increased transcription of the type 1 interferon gene, *IFNB1*, which encodes interferon- β (IFN β). Through a positive feedback loop involving IFN β , JAK1, and signal transducers and activators of transcription 1 (STAT1) and 2 (STAT2), binding of the IFN receptor further up-regulates STING and transcription of other proinflammatory cytokine genes.¹ *In vitro*, JAK inhibitors such as baricitinib can disrupt this positive feedback loop, and they are currently under investigation for the treatment of SAVI and other IFN-mediated inflammatory conditions.¹

STING-induced endothelial-cell dysfunction may activate an inflammatory and vaso-occlusive process resulting in painful distal ulcerative lesions, eschars, and acral violaceous plaques and nodules. Livedo reticularis, Raynaud's phenomenon and nailfold capillary tortuosity have also been reported.¹ In 9 of the 11 reported cases, interstitial lung disease was identified on imaging, although not all patients were symptomatic. Respiratory findings

include recurrent wheezing, pulmonary fibrosis, restrictive lung disease, tachypnea, multifocal lymphoid formations, and interstitial edema.¹ The presence of STING in type II pneumocytes and in alveolar macrophages likely contributes to the pulmonary disease in patients with SAVI, through mechanisms that are not fully understood.

SAVI shares features with antiphospholipid antibody syndrome, cryofibrinogenemia and necrotizing vasculitis, as well as the other interferonopathies such as familial chilblain lupus and Aicardi-Goutières syndrome. The lack of brain involvement and the presence of interstitial lung disease and characteristic destruction of acral/cold-sensitive tissues differentiate SAVI from the latter condition.

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ABBREVIATIONS

STING	Stimulator of interferon genes
SAVI	STING-associated vasculopathy with onset in infancy
IFN	Interferon
cGAMP	Cyclic guanosine monophosphate-adenosine monophosphate
TBK1	TANK-binding kinase 1
IRF-3	Transcription factor interferon receptor factor 3
STAT	Signal transducers and activators of transcription
JAK	Janus kinase

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KEY TEACHING POINTS

- SAVI is a recently described interferonopathy resulting from constitutive action of STING and upregulation of IFN β signaling.
- SAVI is characterized by facial erythema with telangiectasia, acral/cold sensitive tissue ulceration and amputations, and interstitial lung disease. It has overlapping features with Aicardi-Goutières syndrome and familial chilblain lupus.
- Traditional immunosuppressive medications and biologic therapies appear to be of limited benefit, but JAK inhibitors may impact disease progression.

Fig 1.
SAVI. Cartilage destruction and scarring on the left helix at the site of previous ulceration.

Fig 2.
A and B, SAVI. Hyperkeratotic scale and multiple erosions, ulcerations and digit amputations.

Fig 3.

Histopathology of hyperkeratotic plaques on knees in SAVI syndrome. **A**, Dilated vessels in papillary dermis with large thrombi. **B**, Mild perivascular lymphocytic infiltrate with rare neutrophils and mild karyorrhexis. (**A** and **B**, Hematoxylin-eosin stain; original magnifications: **A**, x40; **B**, x400.)

Table 1

Previously reported STING-associated vasculopathy with onset in infancy (SAVI) patient demographics and clinical findings.

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8	Patient 9	Patient 10	Patient 11
Sex	Male	Male	Male	Male	Female	Male	Female	Male	Female	Male	Male
Age of onset	Adult	Teenage	Teenage	Infancy	Neonatal	8 weeks	6 weeks	1 week	Neonatal	3 days	8 weeks
Status	Alive	Died	Alive	Alive	Alive	Died	Alive	Alive	Died	Alive	Alive
Failure to thrive	+	+	+	+	+	+	+	+	+	+	+
Interstitial lung disease	-	+	+	+	+	+	+	-	+	+	+
Arthralgia/arthritis	+	+	+	-	-	+	-	-	+	-	NR
Distal ulceration	NR	NR	NR	NR	+	+	+	+	+	+	+
Malar rash	-	+	+	+	+	+	+	+	+	+	+
Gene mutation	V155M	V155M	V155M	V155M	N154S	V155M	N154S	V147L	N154S	N154S	V147M
Mutation type	De novo	Inherited	Inherited	Inherited	De novo	De novo	De novo	De novo	De novo	De novo	De novo

NB: Patients 1-4 were of the same kindred and exhibited an autosomal dominant inheritance pattern. Patients 1-4 from Jeremidh, et al.² Patients 5-10 from Liu, et al.¹ Patient 11 from Munoz, et al.³ NR = not reported.