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

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Key words: autoinflammation; autoinflammatory; gangrene; genodermatosis; inflammation; interferonopathy; interstitial lung disease; vasculitis.

CASE SUMMARY

History

An 18-year-old Turkish man 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 lower extremities. His previous therapies included intravenous methylprednisolone, iloprost, pentoxifylline, acetylsalicylic acid, stanozolol, azathioprine, and nifedipine without benefit.

The patient had a fraternal twin brother 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

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Conflicts of interest: None declared.

Editor's note: Dr Goldbach-Mansky at the National Institutes of Health (NIH) 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.

Dr Chia evaluated this patient during an elective rotation at the National Institutes of Health.

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Abbreviations used:

IFN: interferon
JAK: Janus kinase
NIH: National Institutes of Health
SAVI: stimulator of interferon genes–associated vasculopathy with onset in infancy
STING: stimulator of interferon genes

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 thousand/μL (normal, 4.23-9.07 thousand/μL) with an absolute neutrophil count of 6.32 K/μL (normal, 1.78-5.38 thousand/μL) 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 thousand/μL (normal, 161-347 thousand/μL). Autoimmune workup revealed an elevated erythrocyte sedimentation rate of 89 mm/h, with a positive antinuclear antibody (1.4 U, normal <1 U), anti-double-stranded DNA antibody and lupus anticoagulant, weakly positive antiproteinase-3 antibody, and negative antimyeloperoxidase antibody and anticardiolipin antibody (IgG, IgM). An elevated 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 of the chest showed diffuse hyperinflation, ground-glass opacity, diffuse cystic changes in a subpleural and anterior lung distribution, along with 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

A diagnosis was made of stimulator of interferon (IFN) 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 Janus kinase (JAK) inhibitor baricitinib for the treatment of autoinflammatory diseases (Clinical Trials.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,

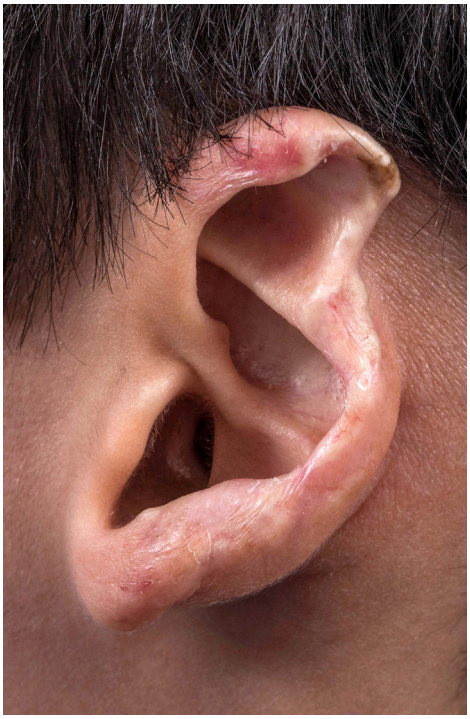

Fig 1. Stimulator of interferon genes–associated vasculopathy with onset in infancy. Cartilage destruction and scarring on the left helix at the site of previous ulceration.

severe cutaneous vasculopathy, and interstitial lung disease and was first described in 2014.[1] To date, there have been 11 published cases (Table I) 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 aspect of the 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 IFN response to synthetic and viral double-stranded