Case Report/Case Series

Stimulator of Interferon Genes–Associated Vasculopathy With Onset in Infancy
A Mimic of Childhood Granulomatosis With Polyangiitis

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IMPORTANCE The type I interferonopathies comprise a recently recognized group of mendelian diseases characterized by an upregulation of type I interferon signaling. These monogenic phenotypes include classic Aicardi-Goutières syndrome and syndromic forms of systemic lupus erythematosus, including familial chilblain lupus and spondyloenchondrodysplasia. Dermatologic features provide a major diagnostic clue to this disease grouping, as exemplified by the recently described stimulator of interferon genes–associated vasculopathy with onset in infancy (SAVI) caused by gain-of-function mutations in *TMEM173*.

OBSERVATIONS We describe a male child who, from the age of 2 months, had significant cutaneous disease that manifested as red violaceous plaques of the cheeks, nose, ears, fingers, and toes that progressed to gangrenous necrosis. In addition to his severe cutaneous vasculopathy, he experienced recurrent fevers, interstitial lung disease, and failure to thrive. His clinical syndrome was refractory to multiple immunosuppressive therapies. Evidence of marked upregulation of type I interferon signaling was observed in peripheral blood, and genetic testing identified a de novo germline mutation in *TMEM173*, confirming a diagnosis of SAVI 7 years after the onset of his disease.

CONCLUSIONS AND RELEVANCE This observational report describes a new case of SAVI, a recently defined monogenic inflammatory phenotype, that exemplifies an emerging group of disorders related to primary upregulation of type I interferon signaling.

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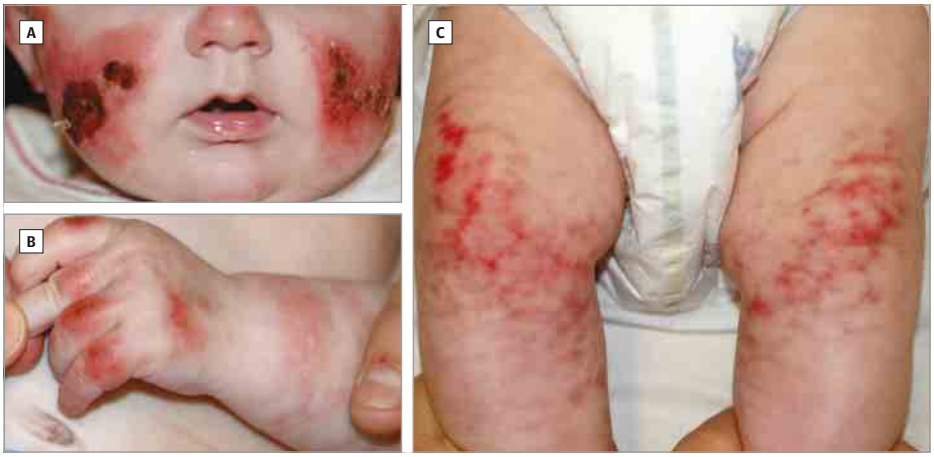
The type I interferonopathies are a newly considered group of monogenic inflammatory diseases that share a common pathogenesis related to an upregulation of type I interferon signaling.[1] This group of conditions includes Aicardi-Goutières syndrome, familial chilblain lupus, spondyloenchondysplasia, and the phenotypes associated with mutations in *PSMB8*. Stimulator of interferon genes (STING)-associated vasculopathy with onset in infancy (SAVI) is a recently described type I interferonopathy with early-onset inflammation manifesting as cutaneous vasculopathy and pulmonary inflammation.[2,3] We describe a new case of SAVI, highlighting the differential diagnosis with childhood granulomatosis with polyangiitis (GPA; previously known as Wegener granulomatosis).

Report of a Case

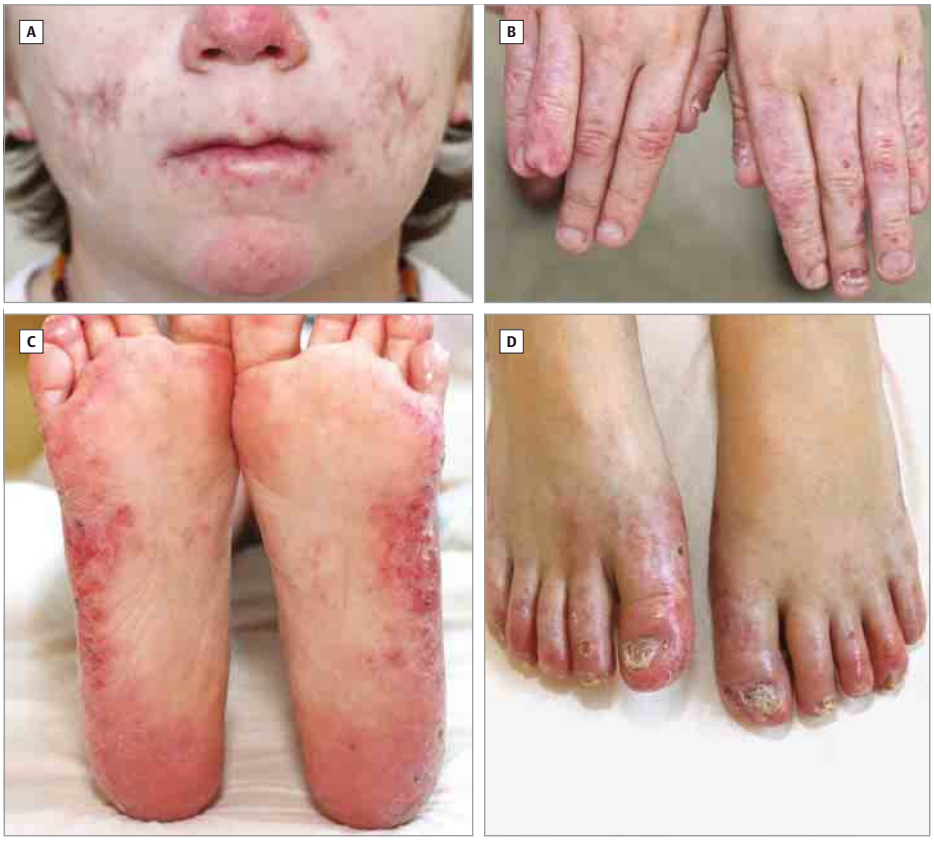
This male child was born at 38 weeks of gestation after a normal pregnancy with intrauterine growth restriction. His birth weight was 2700 g, length was 45 cm, and head circumference was 32 cm (all under the fifth percentile). Cutaneous features developed at approximately 8 weeks of age, with purple-red infiltrated and telangiectatic plaques, and sometimes with pustula that affected the cheeks, helix and lobule of the ears, tip of the nose, and dorsal side of the hands, fingers, and toes. He was also noted to have a reticulated patterning of the limbs. Rapid development of large eschars and secondary painful crusts on the cheeks and the tip of the helix were observed (**Figure 1**). These features worsened every winter according to cold exposure, with 3 to 4 cutaneous flare-ups per year associated with high temperatures that lasted approximately 7 to 10 days. Three histologic analyses of the telangiectatic plaques (3-mm biopsy specimens) revealed rare epidermal apoptotic keratinocytes and perivascular lymphocytic and neutrophilic infiltrates with nuclear dust (leukocytoclasia) throughout the entire dermis without damage to the vessel wall, fibrinoid necrosis, and thrombi. The results of direct immunofluorescence of lesional skin were negative. At the age of 3 months, he was also noted to be tachypneic. High-resolution

Figure 1. Stimulator of Interferon Genes–Associated Vasculopathy With Onset in Infancy Cutaneous Manifestations



A and B, At 5 months of age, erythematous and violaceous infiltrated plaques that affected the cheeks with central cutaneous ulcerations and eschars, the tip of the nose, the helix and lobule of the ears, and the dorsal side of the hands and fingers. C, A reticulate and inflammatory livedo of the limbs, predominating around the knees, was also noted.

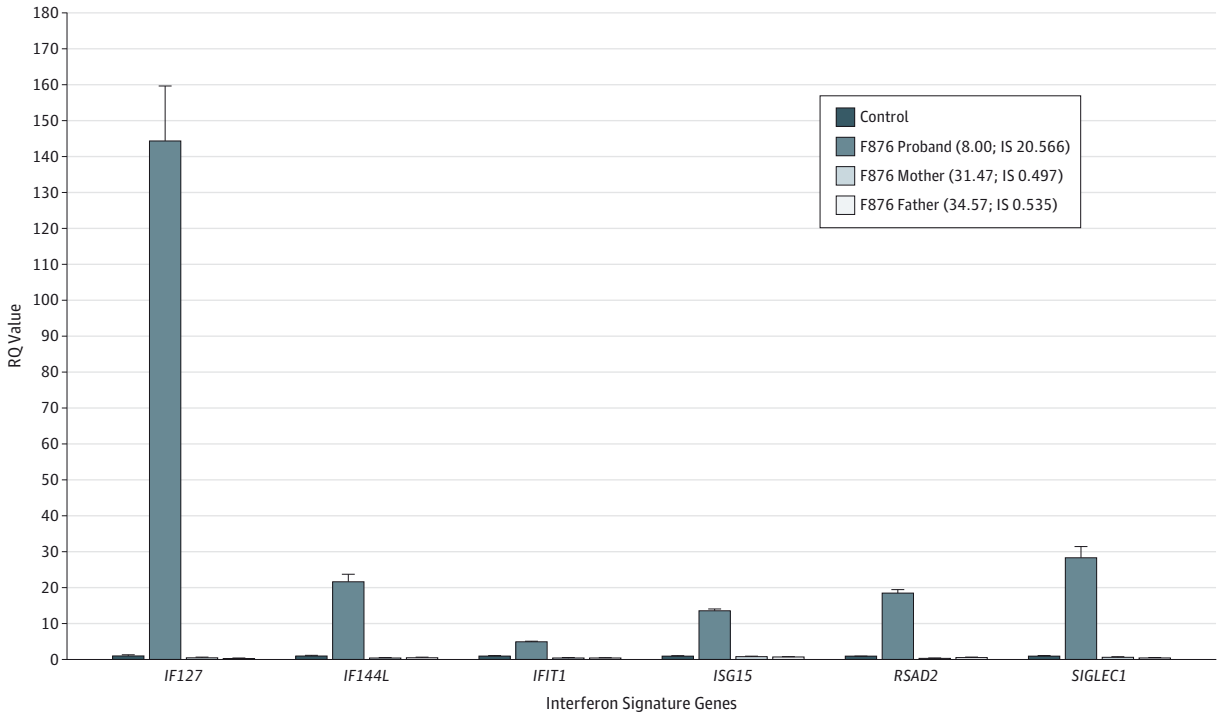
Figure 2. Stimulator of Interferon Genes–Associated Vasculopathy With Onset in Infancy Cutaneous Manifestations at 7 Years of Age



A-C, Facial telangiectatic lesions on the nose, cheeks, chin, and perilabial area associated with violaceous, scaling, and atrophic plaques on the hands and feet (predominantly on the toes and lateral sides). D, Severe nail dystrophy was also present.

computed tomography of the chest revealed interstitial lung disease characterized by diffuse ground glass and reticular opacities with an upper left and lower lung predominance. Bronchoalveolar lavage revealed an inflammatory infiltrate with a large amount of lymphocytes. Routine laboratory examination revealed a normal white blood cell count, hemoglobin level, platelet count, and renal and hepatic function. The erythrocyte sedimentation rate varied from 40 to 67 mm/h (reference range, <20 mm/h), whereas the C-reactive protein level was normal or slightly increased. Lactate dehydrogenase was consistently increased, with levels fluctuating from 549 to 1124 U/L (reference range, 170-450 U/L) (to convert to microkatals, multiply by 0.0167). The results of tests for circulating antinuclear rheumatoid factor, cryoglobulin, cryofibrinogen, cold agglutinins, IgG and IgM antibodies for cardiolipin, β_2-glycoprotein I, and lupus anticoagulant were

Figure 3. Gene Expression Studies



Quantitative reverse transcription–polymerase chain reaction of a panel of 6 interferon stimulated genes (ISGs) in whole blood measured in the proband and his parents compared with healthy controls. The relative quantification (RQ) value is equal to $2^{-\Delta\Delta Ct}$, with $-\Delta\Delta Ct \pm$ SDs (ie, the normalized fold change relative to a calibrator). Each value is derived from 3 technical replicates. Numbers in parentheses refer to decimalized age in years at sampling followed by the interferon score (IS) calculated from the median fold change in the RQ value for the panel of 6 ISGs.

negative. Nontyped antineutrophil cytoplasmic antibodies (ANCA) test results were positive, with levels varying from 1/200 to 1/400 (reference range, <1/100). Considering the clinical presentation of cutaneous inflammatory and necrotic lesions, interstitial lung disease, and the positive ANCA titer results, a diagnosis of childhood protracted superficial GPA was suspected.

He was initially treated with a methylprednisolone bolus, 1.73 g/m^2 for 3 days, followed by oral prednisone, 2 mg/kg with gradual diminution of dose, acetylsalicylic acid (100 mg/d), clopidogrel bisulfate (2 mg/d), and nifedipine (10 mg/d). One month later, computed tomography of the lung revealed improvement with a regression of the ground glass opacification. However, his cutaneous features worsened, leading to partial amputation of the helix and profound ulcerations of the cheeks (which were prominent by 5 months of age). Thus, intravenous immunoglobulins (6 infusions of 1 g/kg per month) were given but with little apparent clinical effect. Mycophenolate mofetil (700 mg/m^2 twice a day during a 4-year period) and hydroxychloroquine (50 mg in 6.5-mg/kg daily dosages) were then introduced. With this regimen, his lung involvement seemed stable, but he continued to experience recurrent episodes of skin necrosis. At 17 months of age, severe gangrene of the right fourth finger necessitated surgical amputation, leading to a trial of 4 consecutive rituximab infusions every week (375 mg/m^2) with prophylactic pentamidine aerosols. Despite this, acute exacerbations with fever and skin damage occurred every winter, although his radiologic pulmonary features remained stable. Treatment with colchicine (1 mg/d for 12 months), methotrexate (0.8 mg/kg per week for 8 months), and chloroquine (50 mg/d in 4-mg/kg daily dosages for 30 months) were considered ineffective. Because of poor growth, with weight and height below the fifth percentile, and despite a normal growth hormone level (insulinlike growth factor 1134 ng/mL [to convert to nanomoles per liter, multiply by 0.131]), somatropin growth hormone treatment was introduced at 6 years of age. Oral prednisone resulted in partial remission of his cutaneous lesions, with corticosteroid dependence estimated at 7.5 mg/d (0.5 mg/kg daily). However, this did not prevent the further development of erythema and necrotic lesions of acral areas, particularly during the winter. Over time there was an evolution of telangiectasia on the nose, cheeks, chin, and perilabial region, with violaceous scaling and atrophic plaques on the hands and feet located predominantly on the toes and lateral sides with nail dystrophy (**Figure 2**). Nasal septum perforation occurred at 6 years of age. Histologic analysis of a nasal septum biopsy was unhelpful, revealing only a nonspecific polymorphic inflammatory infiltrate without perivascular distribution and an absence of vasculitis or granulomatosis. At this point, his pulmonary lesions remained stable from a radiologic perspective. No pulmonary biopsy was ever performed.

Considering the possibility of a type I interferonopathy, we recorded an increase of interferon alfa activity in the serum

Table. Cutaneous Involvement and Other Main Features Associated With Currently Recognized Type I Interferonopathies

Variable	AD			AR	
	SAVI	Familial Chilblain Lupus	Aicardi-Goutières Syndrome	Spondyloenchondromatosis	*PSMB8*-Related Disease
Inheritance/gene	*TMEM173*	*TREX1*, *SAMHD1*	AR/ *TREX1*, *RNASEH2A/B/C*, *SAMHD1*, *ADAR*, *IFIH1* AD/ *TREX1*, *ADAR*, *IFIH1*	*ACP5*	*PSMB8*
Cutaneous manifestations					
Chilblainlike lesions	Yes	Yes	Yes	Yes	Yes
Digital amputations	Yes	Yes	Yes	Yes	NR
Contractures	No	Yes (particularly fifth fingers)	Yes	No	Yes
Ear tissue loss	Yes	Typical	Typical	NR	NR
Panniculitis	No	No	Occasional	No	Yes
Lipoatrophy	No	No	No	No	Yes
Freckling	No	No	Noted with mutations in *ADAR* and *IFIH1*	No	No
Other clinical and biological anomalies					
Neurologic involvement	NR	Disease-associated developmental delay and intracranial calcification reported in some family members	Typically, severe neurologic disease with developmental delay and intracranial calcification	Developmental delay with intracranial calcification and spastic paraparesis reported in a small proportion of cases	Intracranial calcification reported in several cases
Lung involvement	Yes	No	No	No	No
Autoimmunity	Variable lupuslike	Infrequent	Infrequent	Common (in particular, systemic lupus erythematosus and autoimmune cytopenias)	No
Other diagnostic indicators	Recurrent fevers; nasal septum perforation	No	Recurrent fevers in initial stages of disease; glaucoma	Skeletal dysplasia (in particular systemic lupus erythematosus)	Recurrent fevers

Abbreviations: AD, autosomal dominant; AR, autosomal recessive; NR, not reported; SAVI, stimulator of interferon genes–associated vasculopathy with onset in infancy.

(19 IU/L; reference range, <2 IU/L), and a significant overexpression of interferon-stimulated genes, a so-called interferon signature, was observed in peripheral blood (**Figure 3**). After the initial description of SAVI, genetic analyses confirmed a heterozygous somatic mutation (c.439G>A, p.V147M) in exon 5 of *TMEM173,* the gene encoding STING. This mutation occurred de novo; accordingly, neither parent had an interferon signature.

Discussion

SAVI is a newly described autoinflammatory disease that occurs due to heterozygous mutations of *TMEM173*, encoding STING. SAVI-related *TMEM173* mutations confer a gain of function on STING, leading to a chronic induction of type I interferon signaling. This clinical syndrome was initially described in a series of 6 cases characterized by systemic inflammation with fever, clinical features of cutaneous vasculitis and microthrombotic angiopathy, and interstitial lung disease.[2] Considering the clinical features previously reported and those described here, we provisionally suggest that 3 consecutive and intricately linked evolutive phases of SAVI can be distinguished. Cutaneous lesions typically begin in the neonatal period or shortly thereafter (<6 months of age), which can be reminiscent of chilblains, being characterized by erythematous to red-purple, sometimes purpuric, plaques present on acral areas, including the fingers, toes, tip of nose, cheeks, and ears (helix and lobule). Telangiectasia, pustules, finger swelling, acral or limb livedo reticularis, and tachypnea are variably associated. At this time, the presence of low-grade fever and systemic biological inflammation with increased levels of acute-phase reactant proteins (erythrocyte sedimentation rate and C-reactive protein) can be seen. Subsequently, these cutaneous lesions progress, with flare-ups worsened by cold weather, the development of punched-out skin ulcerations of variable sizes, eschars, and digital gangrene, which can lead to surgical amputation. This cold sensitivity, mentioned in the original series and highly reminiscent of the chilblains seen in Aicardi-Goutières syndrome and familial chilblain lupus, was striking in our case, with a seasonal rhythmicity and absence of cutaneous flare-ups and fever episodes during the warmer months. The last, more chronic stage is marked by the progressive development of atrophic and depigmented scars with telangiectasia of the extremities and nail alterations, including nail plate disruption, onycholysis, and severe onychodystrophy, resulting in partial or complete destruction of the nail plates.

The results of histologic analyses of lesional skin biopsy specimens were poorly contributive in our case, indicating non-

specific dermal perivascular inflammation with karyorrhexis in the absence of vasculitis or microthrombotic vascular changes. This finding could be due to the small size of the biopsy specimens taken and the disease stage at the time of examination.

In the context of skin inflammatory and necrotic lesions that primarily affected acral areas with systemic inflammation, several differential diagnoses could be evoked, including childhood-specific necrotizing vasculitis, antiphospholipid syndrome, cryoglobulinemic vasculitis, and thrombotic vasculopathy associated with cryofibrinogenemia. In our case, the association of the skin lesions with interstitial lung disease; positive titers of ANCA, although not typed; and subsequent nasal-septum perforation led us to consider the diagnosis of childhood limited and/or protracted superficial GPA.[4,5] Nevertheless, some clinical and biological data appeared discordant with this diagnosis, including the extreme rarity of perinatal-onset GPA, the absence of other skin lesions encountered during childhood GPA (eg, vesicles and bullae, erythema nodosum, and pyoderma gangrenosum–like lesions), the absence of histologic granulomatous inflammation in skin or nasal biopsy specimens, and negativity of myeloperoxidase- and proteinase 3–specific ANCA.[6] However, the presence or absence of specific ANCA does not appear to be a formal discriminating criterion between SAVI and GPA because cytoplasmic ANCA positivity was reported, albeit transiently and at low titer, in 2 of 6 cases of SAVI.[2]

The pulmonary manifestations observed in our case were consistent with the previously described cases of SAVI but differed in the absence of paratracheal adenopathy. Of interest, an improvement of the imaging features of interstitial lung disease on computed tomography was observed after treatment with methylprednisolone pulses and mycophenolate mofetil, although this treatment regimen failed to halt the progression of our patient's skin lesions. Other treatments, including intravenous immunoglobulins, methotrexate, rituximab, colchicine, antimalarials, low-dose acetylsalicylic acid, clopidogrel, and nifedipine, were all considered ineffective, as previously reported.[2]

Clinical cutaneous phenotypic overlap between SAVI and the other interferonopathies is of particular interest from a pathophysiologic point of view. All these disorders, including familial chilblain lupus[7]; Aicardi-Goutières syndrome,[1,8] where skin lesions can be particularly prominent in the context of *SAMHD1* mutations; spondyloenchondysplasia[9]; and *PSMB8*-related disease,[10,11] can demonstrate the early onset of chilblainlike lesions, acral vasculitis, and gangrene with varying degrees of severity (**Table**). Although no simplistic pathogenic explanation can be provided at this time, the direct effect of interferon alfa could account for the development of cold-sensitive skin lesions in areas of low flow and distal circulation, such as the fingers, toes, nose, and ears. Of note, interferon therapy has been previously associated with skin inflammatory and ischemic complications, including cutaneous digital necrosis, vasculitis-like syndrome, Raynaud phenomenon,[12] and atrophie blanche.[13,14] A direct vasoconstrictive effect and increased procoagulant activity induced by the local hyperproduction of interferon in endothelial cells[14] could account for the vascular damage observed in SAVI. Similarly, interstitial pneumonitis, with radiologic anomalies close to SAVI pulmonary-related disease, has been reported after interferon therapy.[15] The pulmonary tropism of SAVI presumably relates to the expression of STING in alveolar macrophages and pneumocytes.[2,3]

Conclusions

In the context of early-onset chilblains and acral vasculitis or gangrene, we suggest searching for increased interferon alfa activity in serum and interferon-stimulated gene transcripts in peripheral whole blood (a so-called type I interferon signature) to determine a diagnosis of a type I interferonopathy.

ARTICLE INFORMATION

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NOTABLE NOTES

Dermatology and the American Experience in Space

Walter H. C. Burgdorf, MD; Leonard J. Hoenig, MD

For over a half century, the American space program has dazzled us with spectacular achievements, such as the Apollo lunar landings and the Space Shuttle missions. These great accomplishments were made possible by the talented NASA personnel, the support of the American public, and the courage of our astronauts, some of whom gave their lives in the pioneering efforts into space. This Notable Note pays tribute to all persons who have contributed to the success of the US space program as it looks at some of the dermatologic lessons learned along the way.

Space flight exposes the skin to the effects of microgravity and the possible exposure to hazardous solar and cosmic radiation, among a number of other concerns. The early space missions were of relatively short duration, typically 17 days or less. Thus, no long-term dermatologic studies on astronauts in space could be performed until the development of space stations, such as the International Space Station, which have allowed astronauts to stay in space for many months.

Dermatologic complaints by astronauts have been recorded by NASA over the years and fortunately have not been serious in nature. Some skin problems were readily explainable, as when the commander of the Apollo 12 mission developed a mild contact dermatitis from the biosensor electrolyte paste.[1] The causes of other symptoms were less clear, as when astronauts at the International Space Station complained of dry, itchy, and thinning skin; increased sensitivity; delayed wound healing; and an increased tendency to skin infections.[2]

Concerning skin cancer, a longitudinal study of health in 312 US astronauts found 33 diagnoses of basal cell and localized squamous cell carcinomas of the skin.[3] This represented a higher than 3-fold increase in prevalence in these nonmelanoma skin cancers over a comparison sample, which is statistically significant. The astronauts did have histories of spending considerable time outdoors for both training and recreation. It is therefore difficult to know if time in space was a contributing factor to the astronauts' skin cancer risk. Two diagnoses of malignant melanoma were made in the astronaut group.

Recently, the first study on changes in skin physiology in space was performed in an astronaut aboard the International Space Station.[2] Skin physiological measurements were taken before, during and after a long-term mission. The inner forearms were studied; one side was treated with a skin protection cream. The measurements revealed a thinned stratum corneum, impaired barrier function, and loss of dermal elasticity. The treated side showed fewer changes. The causes of these epidermal and dermal alterations are unknown. Further dermatologic studies are currently under way at the International Space Station.

Today, we can only but imagine at what the future holds in store for the American space program. Whatever our next missions beyond Earth may be, their success depends on the ability of the human body and its skin to adapt to the challenges it will face as America continues its incredible journeys into space.

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