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【 CASE REPORT 】

Stimulator of Interferon Genes-associated Vasculopathy with an Onset in Infancy Diagnosed after the Development of Atypical Pulmonary Lesions During Treatment as Juvenile Idiopathic Arthritis

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Abstract:

An 18-year-old man showed swelling, pain, and limited motion of the hand, knee, and foot joints without X-ray abnormalities at 2 years old (X-16). In X-12, interstitial pneumonia was observed. He was diagnosed with juvenile idiopathic arthritis associated with interstitial pneumonia and received immunosuppressive therapy. However, interstitial pneumonia progressed, and in X-2, he was referred to our hospital. Whole-exome sequencing and an *in silico* analysis revealed a gain-of-function mutation in *TMEM173* (p.R281Q), and he was diagnosed with stimulator of interferon genes (STING)-associated vasculopathy with onset in infancy (SAVI). We encountered the first SAVI case in Japan.

Key words: stimulator of interferon genes, STING-associated vasculopathy with onset in infancy, juvenile idiopathic arthritis, interstitial pneumonia

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Introduction

The concept of stimulator of interferon genes (STING)-associated vasculopathy with onset in infancy (SAVI) was first proposed by Liu et al. in 2014. SAVI is a rare inflammatory disease characterized by systemic inflammation via the overproduction of type I interferon (IFN) due to gain-of-function mutations in STING (1). STING is a transmembrane protein on the endoplasmic reticulum that induces the production of IFNs against viral DNA infection and the expression of IFN-related genes by activating an immune response through STING signaling (2).

Several mutations in the *TMEM173* gene that encodes STING have been reported. In 2014, p.V147 L, p.N154S, and p.V155M were identified. Subsequently, p.V147M, p.G166E, p.C206Y, p.R281Q, and p.R284G were reported. However, the precise molecular mechanism of STING mutants in patients with SAVI remains unclear.

To date, approximately 30 cases of SAVI have been reported worldwide. Major clinical symptoms include systemic inflammatory manifestations (a fever, elevated immune response), skin symptoms, such as nail defect/dysplasia and finger gangrene, and respiratory symptoms mainly associated with interstitial lung disease (1, 3-11). There is presently no established treatment protocol for SAVI. However, based on its pathogenesis, Janus kinase (JAK) inhibitors are expected to be effective. In fact, a small number of studies have reported the effectiveness of this intervention (3, 12).

We herein report a patient who developed atypical pulmonary lesions during treatment for juvenile idiopathic arthritis (JIA) and was ultimately diagnosed with SAVI.

Case Report

An 18-year-old Japanese man visited our hospital for res-

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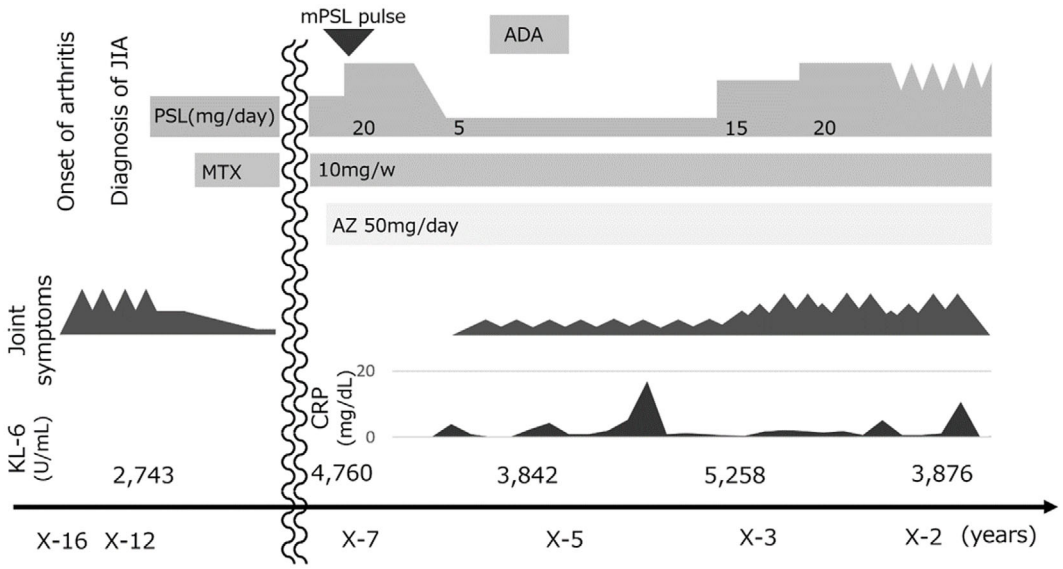

Figure 1. Clinical history until referral to our department. JIA: juvenile idiopathic arthritis, ADA: adalimumab, PSL: prednisolone, mPSL: methylprednisolone, MTX: methotrexate, AZ: azathioprine

piratory discomfort and joint pain. At 2 years old (X-16), the patient had swelling, pain, and limited range of motion of the hand, knee, and foot joints and been examined at a local orthopedic clinic.

X-ray imaging had shown no abnormalities, and he had been followed up without treatment. However, his joint-related symptoms persisted. In X-13, he had contracture of bilateral hand joints, pain in the left shoulder joint, and neck pain. Concurrently, he also developed dyspnea, and in X-12, he was admitted to the Department of Pediatrics at our hospital for a detailed examination.

Plain chest X-ray and computed tomography (CT) showed significant interstitial pneumonia, and his Krebs von den Lungen (KL)-6 level had significantly increased to 2,743 U/mL. Based on the persistent multiple joint symptoms, the patient was diagnosed with JIA associated with interstitial pneumonia, and treatment was started with glucocorticoid (GC) and methotrexate (MTX). The joint symptoms resolved with the treatment, but the interstitial changes in the lungs gradually progressed.

In X-11, he was found to have a synovial cyst on the dorsum of the hand and was suspected of having early-onset sarcoidosis (EOS). However, granulomas were not observed, and genetic testing showed no mutations associated with EOS. In X-7, combination therapy with azathioprine was started, and GC pulse therapy was also administered. However, his interstitial pneumonia continued to progress, and general malaise and multiple joint pain were exacerbated by the reduction in the dose of GC. In X-5, the tumor necrosis factor (TNF) inhibitor adalimumab was started but discontinued after several months because of an increase in the KL-6 level and its overall ineffectiveness. As with the earlier treatment, the emphysematous changes in the lungs continued to progress gradually, and the joint symptoms were exacerbated by the reduction in the dose of GC. Therefore, in April of X-2, the patient was referred to our department for a further assessment of the diagnosis (Fig. 1, Fig. 2A, B).

In X-2 (the time of his first admission to our department), his height was 140.6 cm, weight was 36.3 kg, body temperature was 36.4 °C, and percutaneous oxygen saturation (SpO_2) was 95% (room air). Chest auscultation revealed fine crackles in the bilateral middle-lower lung fields. There was no tenderness, joint swelling, or rash.

A blood count showed an elevated white blood cell count. There was no elevation of hepatobiliary enzymes, and his renal function was normal. The C-reactive protein (CRP) level was slightly elevated. KL-6 was markedly elevated to 4,597 U/mL. The immunoglobulin (Ig)G level was increased, and the antinuclear antibody titer was 1:320 (homogeneous pattern). However, no disease-specific autoantibodies were found. In addition, myeloperoxidase anti-neutrophil cytoplasmic antibody (MPO-ANCA) and proteinase (PR)3-ANCA titers were elevated (Table 1). X-ray of the hand and foot joints showed no joint space narrowing, bone erosion, or joint destruction. Plain chest X-ray showed a linear shadow in the right middle-lower lung field and hyperlucency in the left middle-lower lung field. Plain chest CT showed significant emphysematous changes in the bilateral lung fields (Fig. 2C).

The present case met the diagnostic criteria for articular-type JIA (the International League of Associations for Rheumatology 2001), as outlined here: A) symptoms of chronic arthritis developing before 16 years old and persisting for at least 6 weeks and arthritis affecting ≥5 joints during the first 6 months of the disease and B) negative test findings for rheumatoid factor (RF) and human leukocyte antigen (HLA)-B27 not tested.

However, a differential diagnosis was also required because the findings were atypical for JIA. Imaging studies did not reveal any joint destruction despite the persistence of

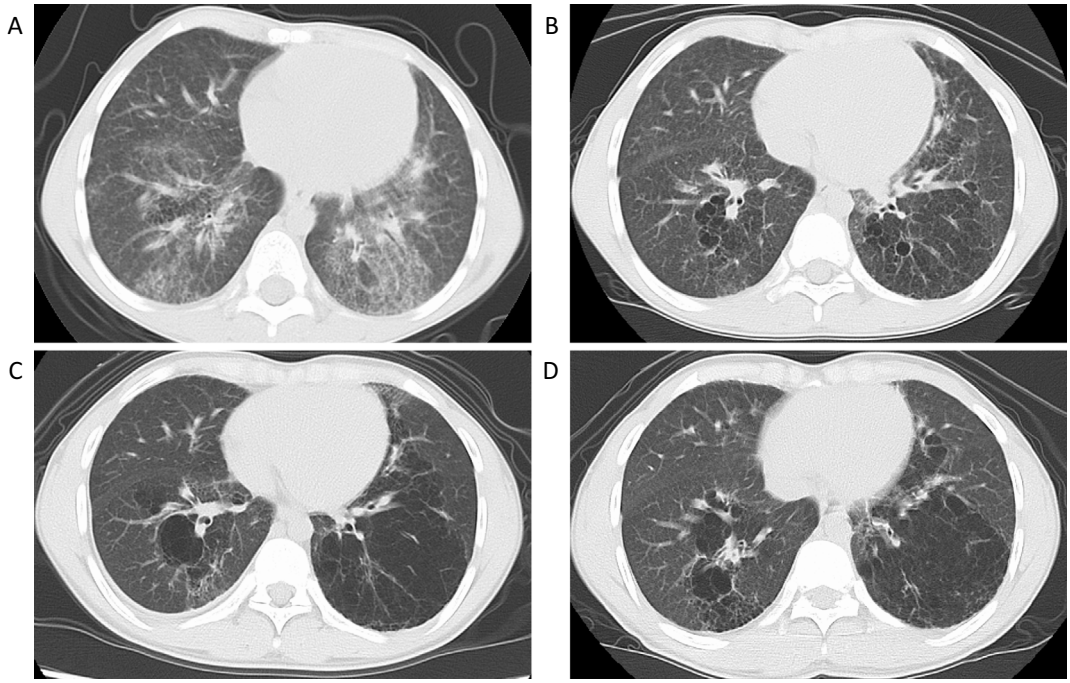

Figure 2. **Plain chest computed tomography findings. A) December of X-13; B) August of X-7; C) April of X-2; and D) June of X. Progression of interstitial pneumonia and emphysematous changes are seen.**

the disease for over 10 years. In addition, the occurrence of interstitial pneumonia is extremely rare in patients with JIA. Therefore, we performed whole-exome sequencing (WES) and an *in silico* analysis of the family (the proband, his father, and unaffected sibling) with the support of the Initiative on Rare and Undiagnosed Diseases in Pediatrics (IRUD-P) to detect genetic causes of autoinflammatory diseases. WES was performed using the SureSelect XT Human All Exon V6 (Agilent Technologies, Santa Clara, USA) for capturing and a HiSeq 2,500 for next-generation sequencing (NGS) with an average read depth of ×100, as previously described (13). During the genome analysis by IRUD-P, tocilizumab was added because it had been difficult to reduce the GC dose. After starting tocilizumab, his joint-related symptoms and inflammatory reaction improved; however, the progressive emphysematous changes in the right dorsal lower lung field persisted (Fig. 2D, Fig. 3).

As a result of the genome analysis among the family by the IRUD-P, in April of X, only the patient was found to have a heterozygous variant in the *TMEM173* gene [NM_198282:c.842G>A, p.(R281Q)], which has been suggested to be a gain-of-function mutation (4). *TMEM173* encodes STING, and mutations in this gene cause SAVI (1). Based on the clinical course and the gain-of-function mutation of *TMEM173* in the patient, a definitive diagnosis of SAVI was made.

Discussion

We described a case of SAVI diagnosed after the development of atypical pulmonary lesions during treatment for JIA. The diagnosis was made with the support of a genetic analysis project for the evaluation of rare and undiagnosed diseases, IRUD-P. In the present case, it took 16 years for an accurate diagnosis of SAVI to be made. In Japan, in 2015, the Japan Agency for Medical Research and Development established the IRUD-P to evaluate rare and undiagnosed diseases. The definitive diagnosis was made with the support of this genome analysis project. When requesting an analysis for this project, the patient information is first provided by the family doctor to the IRUD-P secretariat. The analysis starts after the necessary consent forms, detailed information, and samples have been received. Since a whole-exome analysis is performed, almost all genes, including other auto-inflammatory-related genes, are analyzed in the process.

With regard to SAVI, although the detailed molecular mechanism concerning the STING mutation were not clarified, in previous reports, the p.V147L, p.N154S, and p.V155M mutations were shown to have amino acid substitutions near the dimer-forming site of STING, and stabilization of STING dimer formation was increased in the mutations of p.N154S and p.V155M (1). All of the new STING mutations (p.206Y, p.R281Q, p.R284G) reported in 2017 were also located outside the linker region important for dimer formation (4). These results suggest that in SAVI, the *TMEM173* gene mutation enhances the stabilization of the STING dimer, thereby accelerating type I IFN transcription.

The clinical characteristics of the present case were severe interstitial pneumonia (emphysematous changes), easily relapsing inflammation after lowering the dose of GC, and joint symptoms observed in early childhood. Although skin

Table 1. Laboratory Date.

[Complete blood cell count]		[Serology]	
WBC	11,400 /μL	CRP	0.15 mg/dL
Hb	15.1 g/dL		
Plt	26.4 ×10⁴ /μL	[Immunology]	
		IgG	2,117 mg/dL
[Coagulation]		IgA	88 mg/dL
PT-T	12.4 sec	IgM	61 mg/dL
APTT-T	36.8 sec	C3	113 mg/dL
[ESR]		C4	14 mg/dL
1hour	12 mm	CH50	58 U/mL
[Biochemistry]		[Autoantibody]	
TP	7.4 g/dL	RF	25.7 U/mL
Alb	3.7 g/dL	Anti-CCP antibody	(-)
T.Bil	0.2 mg/dL	Antinuclear antibody	×320
AST	26 U/L	Anti-SS-A antibody	<1.0 U/mL
ALT	36 U/L	Anti-SS-B antibody	<1.0 U/mL
LDH	292 U/L	PR3-ANCA	23 U/mL
ALP	211 U/L	MPO-ANCA	81 U/mL
BUN	13 mg/dL	Anti-dsDNA antibody	2.1 U/mL
Cr	0.59 mg/dL	Anti-Sm antibody	<1.0 U/mL
Na	137 mmol/L	Anti-Scl-70 antibody	<1.0 U/mL
K	3.7 mmol/L	Anti-Centromere antibody	(-)
Cl	103 mmol/L	Anti-U1-RNP antibody	<2.0 U/mL
Ferritin	64 ng/mL		
KL-6	4,597 U/mL	[Infection]	
		HBsAg	(-)
		HBsAb	(-)
		HBcAb	(-)
		HCVAb	(-)
		T-SPOT	(-)

WBC: white blood cell, Hb: hemoglobin, Plt: platelet, PT: prothrombin time, APTT: activated partial thromboplastin time, TP: thyroid peroxidase, Alb: albumin, T-bil: total bilirubin, AST: aspartate aminotransferase, ALT: alanine aminotransferase, LDH: lactate dehydrogenase, ALP: alkaline phosphatase, BUN: blood urea nitrogen, Cr: creatinine, Na: natrium, K: Kalium, Cl: Crawl, KL-6: krebs von den Lungen

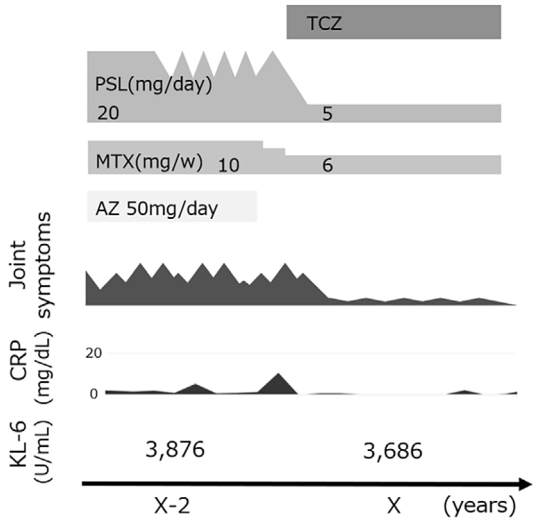

Figure 3. Clinical course after admission to our department. TCZ: tocilizumab, PSL: prednisolone, MTX: methotrexate, AZ: azathioprine

symptoms (nail defect/dysplasia, finger gangrene) have been previously reported in several cases (Table 2), these were not observed in the present case over the 13 years prior to the diagnosis. The patient had joint symptoms, which led to the initial diagnosis of JIA. Among the approximately 30 previous reports, 4 described cases of SAVI with joint symptoms (1, 6, 9); thus, there is a possibility that the joint symptoms without destruction in the present case were due to the early phase of SAVI. Of the patients who developed joint symptoms, one had a p.N154S mutation, and three had p.V155M mutations. Two of the p.V155M mutation patients were monozygotic twins. One patient who had SAVI with a p.R281Q mutation had been reported in the past, but no inflammatory joint condition appeared in the present patient.

When the patient was 18 years old, his height was approximately 140 cm, which was well below (-2.0 standard deviations) the normal height of 18-year-old Japanese men. Based on several reported cases of growth disorder (4, 10), an association between SAVI and growth disorder was sus-

Table 2. Clinical Characteristics of Patients with STING-associated Vasculopathy with Onset in Infancy (SAVI), Including the Present Case.

	Clinical features	Frequency	Our case
Male		59.3%	○
Fever		77.8%	○
Skin	Loss of nail/Dysplasia	85.0%	×
	Digit Gangrene	69.6%	×
Respiratory system	Interstitial pneumonia	92.0%	○
	Respiratory function abnormality	83.8%	○
	Paratracheal Lymphadenopathy	77.8%	×
	Pulmonary fibrosis	76.9%	○
Lab date	Increased inflammatory response	96.3%	○
	Hypergammaglobulinemia	75.0%	○
	Anti-phospholipid antibody	75.0%	×
	Antinuclear antibody	56.5%	○
	PR3-ANCA	28.6%	○

pected. However, the previous cases might all have been treated with GC in early childhood, so the effect of the drug on growth cannot be overlooked. Although the clinical characteristics associated with each mutation are not clear because only a few cases have been reported, both the patient in the present study and a previously reported patient who had the same variant of the gain-of-function mutation (p.R281Q) (4) had severe interstitial pneumonia (emphysematous changes) and significant inflammatory findings. A pathological study of the lung lesions of SAVI reported that there were emphysematous changes just below the pleura and around the respiratory tract, interstitial fibrosis, and aggregation of CD20-positive B cells in the lung parenchyma. No lesions of vasculitis were found. In the lung, STING is expressed on type II alveolar epithelial cells, tracheal cells, and alveolar macrophages. In cigarette smoke-induced chronic obstructive pulmonary disease (COPD) model mice, it has been reported that the enhancement of the STING-type I IFN pathway in the lung promotes the release of remodeling factors and induces the development of emphysema. It may be possible that emphysematous changes developed through this mechanism as well (9, 14). The association between the genetic mutations and clinical characteristics remains unclear, so the further accumulation of cases is needed.

There is no established treatment for SAVI. Previous case reports have described treatment with GC, MTX, TNFα inhibitors (e.g. etanercept and infliximab), anti-CD20 antibody (rituximab), anti-IL-6 inhibitor (tocilizumab), anti-BLyS antibody (belimumab), and acetylsalicylic acid (11). However, these treatments were ineffective or only partially effective. In contrast, JAK inhibitors have been reported to be effective for SAVI (3, 12). JAK inhibitors inhibit the transcription of IFN-stimulated genes via the inhibition of the Janus kinase-signal transducer and activator of transcription (JAK-STAT) signaling pathway by binding to JAK (15, 16). There have been four reported cases of SAVI treated with baricitinib, a JAK inhibitor, in which improvement in vasculitis (skin flare), inhibition of the progression of limb necrosis, stabilization of the respiratory function [including the diffusing capacity of carbon monoxide (DL_{CO})], stabilization of interstitial lung disease, and a reduction in the requirement of GC were reported (12). Another study reported that ruxolitinib, a JAK inhibitor, was effective in reducing the symptoms of interstitial pneumonia, significantly improving the skin symptoms, and lowering the CRP level (3). Because type I IFN plays an important role in the pathogenesis of SAVI, it is highly likely that JAK inhibitors are an effective treatment, and JAK inhibitors deserve further consideration as treatment options in such patients. Anifrolumab, an IFN receptor antibody, also may be a treatment option in the future.

Conclusions

We reported a case in which SAVI was finally diagnosed following the clinical course of atypical pulmonary lesions developing during treatment for JIA. Based on the mechanism of action, JAK inhibitors are expected to be effective in treating the disease. However, further evidence from case reports will be required before this can be recommended as a standard treatment. For the early diagnosis, when a patient shows progressive atypical organ damage, a genome analysis should be performed to evaluate the possibility of an autoinflammatory disease.

Author's disclosure of potential Conflicts of Interest (COI).
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