J Rheum Dis 2024;31(3):182-187
https://doi.org/10.4078/jrd.2023.0075
pISSN: 2093-940X, eISSN: 2233-4718

Case Report

Unraveling the diagnostic odyssey: stimulator of interferon gene-associated vasculopathy with onset in infancy in a 30-year-old female

Hae Ryung Kim, M.D.[1], Seon Hee Lim, M.D.[2], Ji Soo Park, M.D.[1], Dong In Suh, M.D., Ph.D.[1,4], Seungbok Lee, M.D.[1,3], Soo Yeon Kim, M.D.[1,3,4], Jong Hee Chae, M.D., Ph.D.[1,3,4], Seong Heon Kim, M.D.[1,4]

[1]Department of Pediatrics, Seoul National University Children's Hospital, Seoul, [2]Department of Pediatrics, Pusan National University Children's Hospital, Busan, [3]Department of Genomic Medicine, Seoul National University Hospital, [4]Department of Pediatrics, Seoul National University College of Medicine, Seoul, Korea

Stimulator of interferon gene (STING)-associated vasculopathy with onset in infancy (SAVI) is an extremely rare autoinflammatory disease. We present the case of a female Korean patient with early-onset interstitial lung disease who was initially suspected to have systemic lupus erythematosus (SLE) but was ultimately diagnosed with SAVI. The patient exhibited signs of interstitial lung disease and cutaneous manifestations before the age of 1 year and continued to have recurrent fever accompanied by pulmonary infiltrates. Based on positive findings for antibodies associated with SLE, such as antinuclear antibodies and anti-double-stranded DNA, the pulmonary involvement was considered a manifestation of SLE. Another significant symptom was recurrent skin ulceration, which led to partial spontaneous amputation of most of the toes due to inflammation. Given the early onset of interstitial lung disease, severe skin ulcers, and symptoms resembling SLE, autoinflammatory syndrome, especially SAVI was suspected. Following confirmation by genetic testing at age 29 years, the patient was started on tofacitinib, a Janus kinase inhibitor. Despite the prolonged use of multiple immunosuppressive therapies, the patient's lung condition continued to worsen, ultimately requiring lung transplantation. This observational report highlights the importance of considering SAVI as a potential diagnosis when manifestations of interstitial lung disease are observed during infancy. Early proactive treatment is crucial for lung involvement, as this can have long-term effects on patient's prognosis.

Keywords: Systemic lupus erythematosus, Interstitial lung disease, Janus kinase inhibitor, Diagnosis

INTRODUCTION

Stimulator of interferon gene (STING)-associated vasculopathy with onset in infancy (SAVI) is an extremely rare autoinflammatory disease first reported in 2014. SAVI has been confirmed in approximately 60 patients globally [1], with two cases reported in Korea [2,3]. STING is a protein encoded by the *STING1* (previously named *TMEM173*) gene located on chromosome 5 [4]. STING plays crucial roles in detecting cyclic GMP-AMP synthase, inducing interferon synthesis, and regulating innate immune responses [5,6]. Increased *STING1* function is associated with increased production of the STING protein, resulting in excessive inflammatory responses and symptoms of SAVI. SAVI symptoms typically begin within months after birth, mainly manifesting as vascular abnormalities. Characteristic features are rashes on the face, ears, nose, fingers and toes,

Received October 30, 2023; **Revised** February 12, 2024; **Accepted** March 18, 2024, **Published online** April 9, 2024

Corresponding author: Seong Heon Kim, https://orcid.org/0000-0001-8003-3010
Department of Pediatrics, Seoul National University Children's Hospital, Seoul National University College of Medicine, 101 Daehak-ro, Jongno-gu, Seoul 03080, Korea. **E-mail:** E-mail: kimsh22@snu.ac.kr

which progress to ulcers and skin necrosis. Recurrent fever, pulmonary damage, myositis, and joint stiffness can also occur. Pulmonary damage presents as an interstitial lung disease that causing respiratory distress. Treatment options are not well established; however, partial effectiveness has been reported with steroids, methotrexate, mycophenolate mofetil, infliximab, and rituximab. Recently, treatment with Janus kinase (JAK) inhibitors has been reported [3,7,8].

We report a female Korean patient initially suspected of having systemic lupus erythematosus (SLE) but ultimately diagnosed with SAVI.

CASE REPORT

The patient was born full term with a birth weight of 2.78 kg. She was the second child of unrelated parents, with no significant family history. Her sibling was healthy.

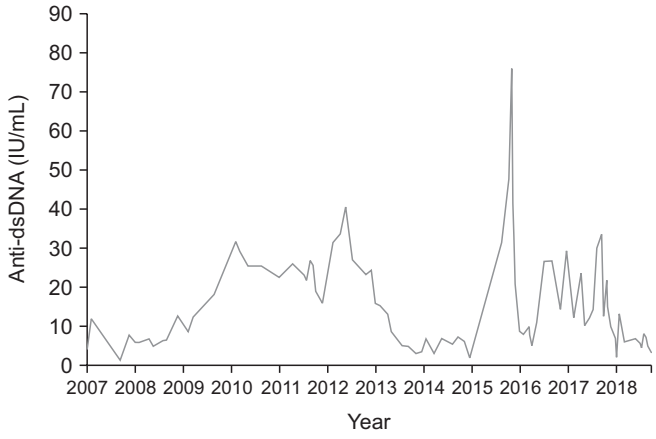

Figure 1. Serum levels of anti-dsDNA antibodies of the patient. Anti-dsDNA: anti-double-stranded DNA.

Cutaneous features developed at age 2 months, with an erythematous rash and pustules on the forehead, cheeks, hands, calves, and toes. These symptoms worsened with cold exposure. The ulcerative lesions worsened with secondary bacterial infections and gradually led to distal necrosis.

The patient was first admitted to a local hospital at 7 months of age with cough, mild fever, and coarse breathing sounds. She had recurrent admissions owing to cough and bilateral perihilar infiltrates on chest radiography. Inflammatory markers were elevated, but microbiological analysis was negative, including for tuberculosis. Treatment with antibiotics failed to relieve the symptoms or improve the radiographic findings. Subsequently, she experienced recurrent infections, including pneumonia, skin infections, parotitis, and acute otitis media.

At age 4 years, she was referred for evaluation of suspected immunodeficiency. She presented with erythematous skin lesions with papules and pustules on her face, palms, fingers, toes, and soles. Laboratory results showed an elevated C-reactive protein level of 5.5 mg/dL (reference range 0 to 0.5 mg/dL) and an erythrocyte sedimentation rate of 81 mm/h (reference range 0 to 20 mm/h). Anti-double-stranded DNA (anti-dsDNA) antibody test results were weakly positive. Anti-dsDNA levels over time are graphed in Figure 1. Hemoglobin levels, white blood cell count, renal function, liver function, T-cell subset percentage, B-cell subset percentage, immunoglobulins, and complement 3 and 4 levels were within the normal range. Fluorescent antinuclear antibody (FANA) was positive with a 1:40 titer, and cytoplasmic anti-neutrophil cytoplasmic antibody (ANCA) was also positive. The results of autoantibodies are summarized in Table 1. Thigh and finger skin biopsies were performed, show-

Table 1. Results of autoantibody tests

	1997	2007	2008	2009	2015	2018	July 2021	Sep 2021
FANA	1:40	1:40	1:80	NA	1:40	1:80	NA	1:40
Lupus anticoagulant	NA	Negative	Negative	NA	Negative	Negative	Positive	NA
C-ANCA	Positive	NA	NA	NA	NA	NA	NA	NA
Anti-cardiolipin Ab	NA	Negative	Negative	NA	NA	Negative	NA	Negative
Anti-beta-2-glycoprotein Ab	NA	Negative	Negative	NA	NA	Negative	NA	Negative
Anti-Ro/La Ab	NA	Negative	NA	NA	NA	NA	Negative	Negative
Anti-RNP Ab	NA	Positive	NA	Positive	NA	Negative	Negative	Equivocal
Anti-Smith Ab	NA	Negative	NA	NA	NA	Negative	NA	Negative
Rheumatoid factor	NA	Negative	NA	NA	NA	NA	NA	NA

FANA: fluorescent antinuclear antibody, C-ANCA: cytoplasmic anti-neutrophil cytoplasmic antibody, RNP: ribonucleoprotein, NA: not available.

ing erythema nodosum and pustular psoriasis, respectively. She was initially treated with tuberculosis medication. Nonsteroidal anti-inflammatory drugs were added because vasculitis was suspected. There was no improvement in symptoms. The patient was lost to follow-up at age 7 years.

At age 13 years, she immigrated to Australia and received ongoing treatment. Physical examination revealed crackles in both lung fields and chest computed tomography (CT) revealed multiple air cysts and subpleural septal thickening in both lungs. A kidney biopsy was performed to evaluate proteinuria, and the pathological findings indicated class II lupus nephritis.

Despite ongoing treatment, the patient's skin lesions worsened, with recurrent bacterial infections. When the patient returned to our center at age 15 years, she presented with multiple ulcerative lesions on her earlobes, tongue, vaginal area, and lower extremities. Nasal septal perforation occurred at 19 years of age, and gangrene of the feet occurred at 21 years of age. Her cutaneous features worsened, leading to partial amputation of the toes (Figure 2).

The patient had dyspnea since age 17 years owing to lung lesions. A pulmonary function test performed at age 18 years showed decreased lung function with a restrictive pattern, and chest CT showed worsening of interstitial lung disease (Figure 2). Despite treatment with multiple immunosuppressants, including prednisolone, methotrexate, mycophenolate mofetil, azathioprine, cyclophosphamide, tocilizumab, cyclosporine A, rituximab, and leflunomide, her symptoms and elevated inflammatory markers did not improve. She was repeatedly hospitalized after age 24 years for worsening dyspnea and prescribed a home oxygen generator at age 25 years. The timeline of the patient's clinical course, tests, and treatments is summarized in Figure 3.

Given the evidence of early onset interstitial lung disease and vasculitic skin lesions, autoinflammatory diseases, particularly SAVI, were strongly suspected. Whole exome sequencing (WES) was performed at age 29 years, and a heterozygous variant of *STING1* (c.439G>A, p.Val147Met) was identified. However, the result was initially classified as a variant of uncertain significance based on the ACMG/AMP (American College of Medical Genetics and Genomic/Association for Molecular Pathology) criteria [9]. Subsequent reports of *STING1* variants associated with SAVI led to a reinterpretation of her WES results as likely pathogenic. Genetic testing of the parents showed that the mutation was *de novo*.

After confirmation of SAVI, she was administered tofacitinib, a JAK inhibitor, to halt disease progression. However, her lung

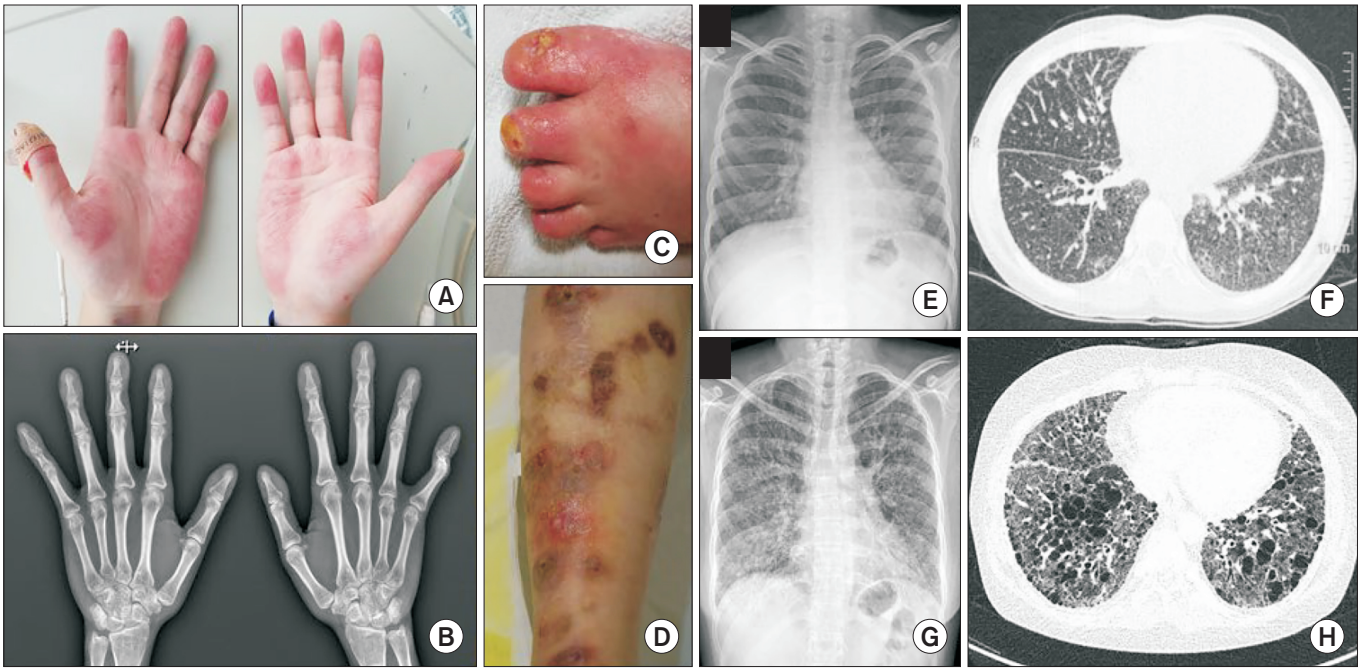

Figure 2. The phenotypes associated with stimulator of interferon gene-associated vasculopathy with onset in infancy (SAVI). (A) Joint contracture of finger, (B) hand both x-ray, (C) partial amputation of toes, (D) ulcerative lesions of calf, (E,F) chest radiograph and computed tomographic scan taken at 15 years of age, and (G,H) chest radiograph and computed tomographic scan taken at 30 years of age.

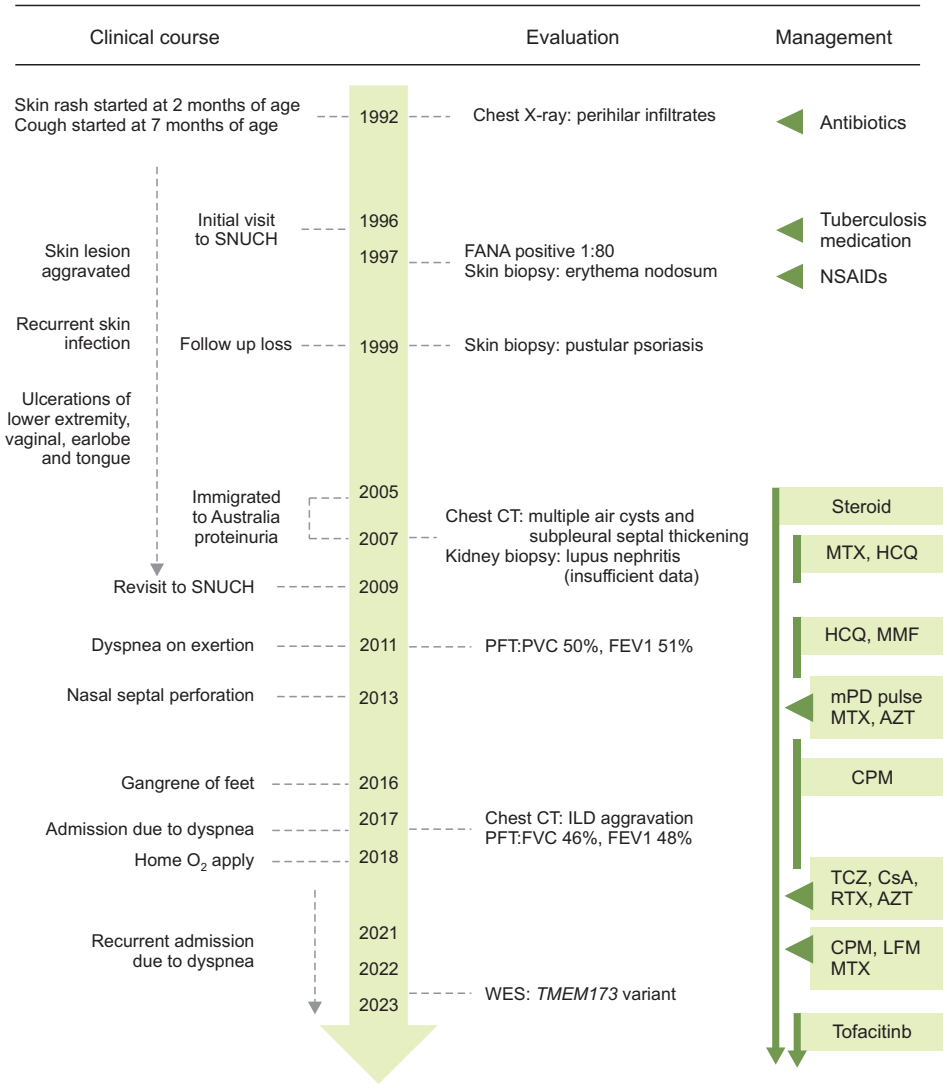

Figure 3. Clinical timeline of the patient. Symptoms, clinical events, results of evaluations, fluctuation of C3 and anti-dsDNA levels, and treatments are listed. SNUCH: Seoul National University Children's Hospital, FANA: fluorescent antinuclear antibody, NSAIDs: non-steroidal anti-inflammatory drugs, CT: computed tomography, PFT: pulmonary function test, PVC: passive vital capacity, FEV1: forced expiratory volume in one second, ILD: interstitial lung disease, FVC: forced vital capacity, WES: whole exome sequencing, C3: complement 3, anti-dsDNA: anti-double-stranded DNA, MTX: Methotrexate, HCQ: hydroxychloroquine, MMF: Mycophenolate mofetil, AZT: azathioprine, CPM: cyclophosphamide, TCZ: tocilizumab, CsA: cyclosporine A, RTX: rituximab, LFM: leflunomide.

condition did not improve. The patient had significant activity limitations due to dyspnea, even when walking less than 100 meters, ultimately requiring a lung.

The study was approved by the Institutional Review Board of the Seoul National University Hospital (IRB no. 2306-038-1437). The requirement to obtain informed consent was waived.

DISCUSSION

SAVI is a newly described autoinflammatory disease caused by gain-of-function mutations of *STING1* that results in sustained activation of type I interferon signaling [10]. SAVI was initially described based on the clinical features of cutaneous vasculitis and interstitial lung disease. We suggest that certain characteristic of SAVI can be distinguished.

Cutaneous manifestations began at an extremely young age, and the presence of ulcerative lesions on the earlobe, nasal septal perforation, and self-amputation due to recurrent ulcerative lesions were particularly alarming. The results of histological analyses of skin biopsy were poorly informative in our case, suggesting nonspecific dermal inflammation in the absence of vasculitis, perhaps owing to the small size of the biopsy specimens obtained. The patient also had recurrent upper respiratory symptoms since early childhood, which were so severe and refractory to treatment that tuberculosis was suspected. Infiltrates were also repeatedly observed on radiographs. In retrospect, these findings were signs of interstitial lung disease that began early in life. Interstitial lung disease in infancy is extremely rare and can be a differentiating factor in the diagnosis of SAVI.

Prior the recent discovery of *STING1* gene mutation in SAVI,

it was previously classified as a monogenic lupus. Therefore, the patient's previous diagnosis of SLE was not entirely incorrect. The positive findings for antibodies associated with SLE supported the diagnosis, and the clinical manifestations were considered manifestations of SLE. However, SAVI has clinical manifestations that are atypical of SLE. SLE is a prototypic autoimmune disease in the pediatric population, particularly in teenage girls; onset before age 5 years is extremely rare. Cases with such early onset are recognized as atypical symptoms and exhibiting a poor response to treatment, resulting in an unfavorable prognosis [11]. Furthermore, a comprehensive evaluation of conditions manifesting with symptoms akin to SLE and commencing before age 5 years is imperative, with a specific focus on monogenic lupus and autoinflammatory syndrome [12]. Considering our patient's case from this perspective, the existence of inflammatory lung and skin lesions before 12 months of age, in conjunction with the presence of autoantibodies, led to the consideration of an autoinflammatory syndrome. The likelihood of SAVI was considered high. However the initial WES was considered a variant of uncertain significance. This highlights the importance of a clear understanding of the clinical features for accurate diagnosis.

Our patient is the third reported case of genetically diagnosed SAVI in Korea. The first patient was a 9-year-old boy with systemic hyper-inflammatory symptoms, including skin lesions, cerebral infarction, and pulmonary dysfunction, who developed sudden left leg weakness and headache at age 5 years [2]. Brain magnetic resonance imaging showed an acute infarction and magnetic resonance angiography showed diffuse advanced luminal irregularities throughout the cerebral arteries. The second case was a 17-year-old girl who had undergone lung transplantation for chronic respiratory failure [3]. She experienced a recurrence of pulmonary hemosiderosis 2 months after lung transplantation. FANA was positive, but other autoantibodies, including anti-dsDNA and ANCA, were negative. All three patients had skin lesions and recurrence of the underlying lung disease started before the age of 1 year, which is inconsistent with autoimmune diseases. However, in the present case, the central nervous system was not involved.

JAK inhibitors can reduce inflammation in SAVI but do not improve irreversible changes in the lungs. Recognizing that SAVI can manifest with early lung involvement is critical for regular follow-up and proactive treatment, as it can significantly affect patients' quality of life.

SUMMARY

We described a case that was initially presumed to be SLE but was subsequently diagnosed as SAVI. These findings emphasize the importance of considering SAVI as a potential diagnosis when interstitial lung disease manifestations present during infancy. Severe recurrent cutaneous ulcers are another significant diagnostic clue. Early proactive treatment is crucial for lung involvement, as this can have long-term effects on patients' prognosis.

FUNDING

None.

ACKNOWLEDGMENTS

To the patient and their family enduring the challenges of rare diseases, we offer words of encouragement, and extend our heartfelt gratitude for their participation in research endeavors aimed at advancing knowledge.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

AUTHOR CONTRIBUTIONS

Conceptualization: H.R.K., S.H.L., S.H.K.; Data curation: H.R.K., S.H.L., S.Y.K.; Supervision: J.S.P., D.I.S., S.L., J.H.C., S.H.K.; Writing: H.R.K., S.H.K.; All authors have read and approved the final version.

ORCID

Hae Ryung Kim, https://orcid.org/0009-0005-4083-2877
Seon Hee Lim, https://orcid.org/0000-0001-8327-7002
Ji Soo Park, https://orcid.org/0000-0002-0522-7736
Dong In Suh, https://orcid.org/0000-0002-7817-8728
Seungbok Lee, https://orcid.org/0000-0002-3145-8714
Soo Yeon Kim, https://orcid.org/0000-0003-2240-3647
Jong Hee Chae, https://orcid.org/0000-0002-9162-0138
Seong Heon Kim, https://orcid.org/0000-0001-8003-3010

REFERENCES

1. Wang Y, Wang F, Zhang X. STING-associated vasculopathy with onset in infancy: a familial case series report and literature review. Ann Transl Med 2021;9:176.
2. Seo J, Kang JA, Suh DI, Park EB, Lee CR, Choi SA, et al. Tofacitinib relieves symptoms of stimulator of interferon genes (STING)-associated vasculopathy with onset in infancy caused by 2 de novo variants in TMEM173. J Allergy Clin Immunol 2017;139:1396-9.
3. Kim D, Song KB, Choi EJ, Yu J. A 17-year-old girl diagnosed with STING-associated vasculopathy with onset in infancy (SAVI) after lung transplantation. Chest 2022;162:e249-52.
4. David C, Frémond ML. Lung inflammation in STING-associated vasculopathy with onset in infancy (SAVI). Cells 2022;11:318.
5. Liu Y, Jesus AA, Marrero B, Yang D, Ramsey SE, Sanchez GAM, et al. Activated STING in a vascular and pulmonary syndrome. N Engl J Med 2014;371:507-18.
6. Jeremiah N, Neven B, Gentili M, Callebaut I, Maschalidi S, Stolzenberg MC, et al. Inherited STING-activating mutation underlies a familial inflammatory syndrome with lupus-like manifestations. J Clin Invest 2014;124:5516-20.
7. Patel S, Jin L. TMEM173 variants and potential importance to human biology and disease. Genes Immun 2019;20:82-9.
8. Lin B, Berard R, Al Rasheed A, Aladba B, Kranzusch PJ, Henderlight M, et al. A novel STING1 variant causes a recessive form of STING-associated vasculopathy with onset in infancy (SAVI). J Allergy Clin Immunol 2020;146:1204-8.e6.
9. Richards S, Aziz N, Bale S, Bick D, Das S, Gastier-Foster J, et al.; ACMG Laboratory Quality Assurance Committee. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med 2015;17:405-24.
10. Munoz J, Rodière M, Jeremiah N, Rieux-Laucat F, Oojageer A, Rice GI, et al. Stimulator of interferon genes-associated vasculopathy with onset in infancy: a mimic of childhood granulomatosis with polyangiitis. JAMA Dermatol 2015;151:872-7.
11. Charras A, Smith E, Hedrich CM. Systemic lupus erythematosus in children and young people. Curr Rheumatol Rep 2021;23:20.
12. Alperin JM, Ortiz-Fernández L, Sawalha AH. Monogenic lupus: a developing paradigm of disease. Front Immunol 2018;9:2496.