

CASE REPORT

Open Access



# Joint contractures responsive to immunosuppressive therapy in a girl with childhood-onset systemic sclerosis double-seropositive for rare anti-nucleolar autoantibodies: a case report

Riki Tanaka<sup>1</sup> , Yumi Tani<sup>1,2</sup>, Yoichiro Kaburaki<sup>1</sup>, Manao Kinoshita<sup>3</sup>, Yasushi Kawaguchi<sup>2</sup>, Yuka Okazaki<sup>4</sup>, Masataka Kuwana<sup>4</sup>, Masayoshi Harigai<sup>2</sup>, Satoru Nagata<sup>1</sup> and Takako Miyamae<sup>1,2\*</sup>

## Abstract

**Background:** Systemic sclerosis (SSc; scleroderma) is an autoimmune connective tissue disease that affects the skin and subcutaneous tissue, in addition to the internal organs of the whole body. Onset in childhood is uncommon; however, both patients with childhood-onset and adult-onset SSc are positive for anti-nuclear antibodies (ANAs). Detection of SSc-related anti-nuclear antibodies is often useful for predicting clinical features, disease course, and outcomes.

**Case presentation:** A 5-year-old Japanese female manifested gradually progressive abnormal gait disturbance, regression of motor development, Raynaud's phenomenon, and the shiny appearance of the skin of the face and extremities at age 2. On admission, she presented a mask-like appearance, loss of wrinkles and skin folds, puffy fingers, moderate diffuse scleroderma (18/51 of the modified Rodnan total skin thickness score), and contracture in the ankle and proximal interphalangeal joints. Grossly visible capillary hemorrhage on nail fold and severe abnormal capillaroscopy findings including bleeding, giant loop and disappearance of capillary consistent with the late phase in SSc. A skin biopsy showed fibrous thickening of the dermis, entrapment of an eccrine sweat glands, and thickened fiber. Chest high-resolution computed tomographic scanning demonstrated patchy areas of ill-defined air-space opacity and consolidation predominantly involving the posterior basilar aspects of the lower lobes presenting with interstitial lung disease. Positive ANA (1:160 nucleolar and homogeneous nuclear staining by indirect fluorescent antibody technique) and double-seropositive for anti-Th/To and anti-PM-Scl antibodies were identified. She was diagnosed with diffuse cutaneous SSc based on the Pediatric Rheumatology European Society/American College of Rheumatology/European League Against Rheumatism Provisional Classification Criteria for (Continued on next page)

\* Correspondence: [tmiyamae@twmu.ac.jp](mailto:tmiyamae@twmu.ac.jp)

<sup>1</sup>Department of Pediatrics, Tokyo Women's Medical University, Tokyo, Japan, 8-1 Kawada-Cho, Shinjuku- Ku, 162-8666 Tokyo, Japan

<sup>2</sup>Institute of Rheumatology, Tokyo Women's Medical University, Tokyo, Japan, 8-1 Kawada-Cho, Shinjuku- Ku, 162-8666 Tokyo, Japan

Full list of author information is available at the end of the article



© The Author(s). 2021 **Open Access** This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit <http://creativecommons.org/licenses/by/4.0/>. The Creative Commons Public Domain Dedication waiver (<http://creativecommons.org/publicdomain/zero/1.0/>) applies to the data made available in this article, unless otherwise stated in a credit line to the data.

(Continued from previous page)

Juvenile Systemic Sclerosis and was successfully treated with immunosuppressive agents, including methylprednisolone pulses and intravenous cyclophosphamide.

**Conclusions:** We experienced the first case of juvenile SSc with anti-PM-Scl and anti-Th/To antibodies. ILD was identified as a typical feature of patients with these autoantibodies; however, diffuse cutaneous SSc and joint contraction were uncharacteristically associated. The case showed unexpected clinical findings though the existence of SSc-related autoantibodies aids in determining possible organ involvement and to estimate the children's outcome.

**Keywords:** Children, Joint contracture, Lung interstitial lesion, Systemic sclerosis, Anti Th/To, Anti-PM-Scl, Autoantibody

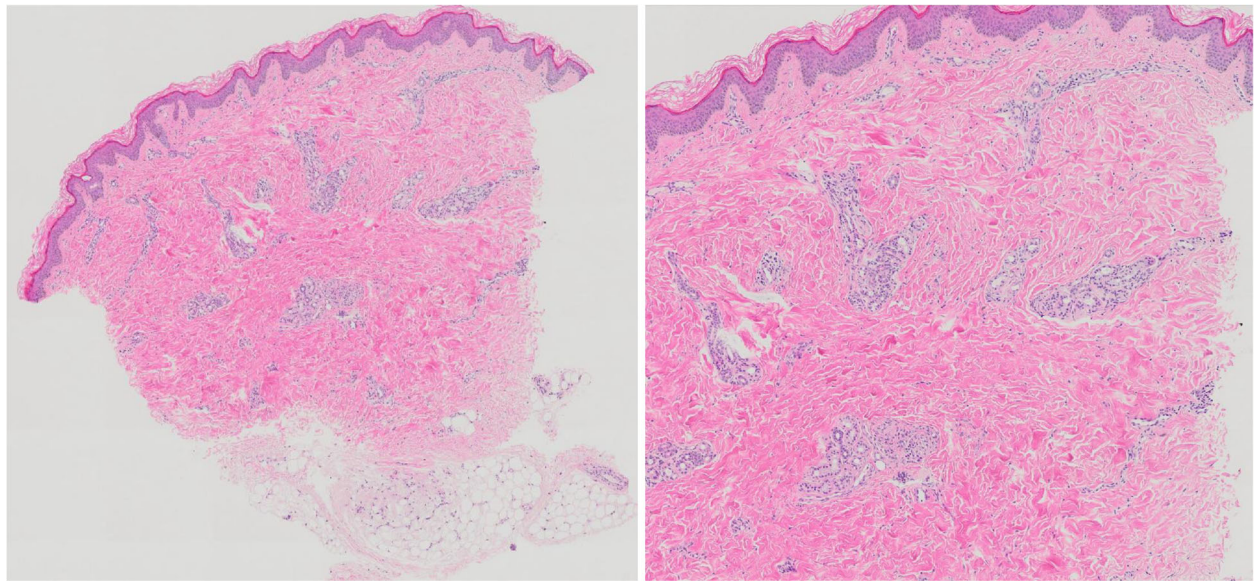
## Background

Systemic sclerosis (SSc; scleroderma) is a heterogeneous and rare autoimmune connective tissue disease that is characterized by immune dysregulation, extensive fibrosis, and vascular dysfunction [1, 2]. It affects internal organs such as the lungs, heart, gastrointestinal tract, and kidneys in addition to the skin and subcutaneous tissue. SSc is more common in women and the peak age of onset is between 20 and 50 years, although the disorder has been described in both young and elderly patients [3–5]. Onset in childhood is uncommon, and children younger than 10 years of age account for approximately 3 % of all cases, and patients between 10 and 20 years of age account for only 1.2–9 % [5]. Childhood onset occurs at a mean age of 8.1 years, and the peak age is between 10 and 16 years [6–8]. Diffuse cutaneous SSc (dcSSc) develops with equal frequency in boys and girls younger than 8 years old, whereas girls outnumber boys 3 to 1 for disease onset occurring in children older than 8 years [9]. Childhood-onset SSc, as compared with adulthood-onset SSc, is predominantly associated with dcSSc, calcinosis ( $p < 0.001$ ), myositis ( $p = 0.050$ ), and lower frequencies of internal organ involvement, such as interstitial lung disease (ILD,  $p = 0.050$ ), pulmonary hypertension ( $p = 0.035$ ), and esophageal involvement ( $p = 0.005$ ) [10]. Anti-nuclear antibodies (ANAs) are frequently detected in patients with childhood-onset SSc as well as in those with adult-onset SSc. Although the role of ANA in the pathogenesis of SSc remains unclear, detection of SSc-related ANAs is useful for predicting clinical features, disease course, and outcomes. Herein, we report a girl with childhood-onset SSc positive for both anti-Th/To and anti-PM-Scl antibodies presenting prominent dcSSc with joint contractures and ILD.

## Case presentation

The patient was a 5-year-old Japanese female, with no known relevant family history, showed gradually progressive abnormal gait disturbance, regression of motor development, Raynaud's phenomenon, and the shiny appearance of the skin of the face and extremities at the

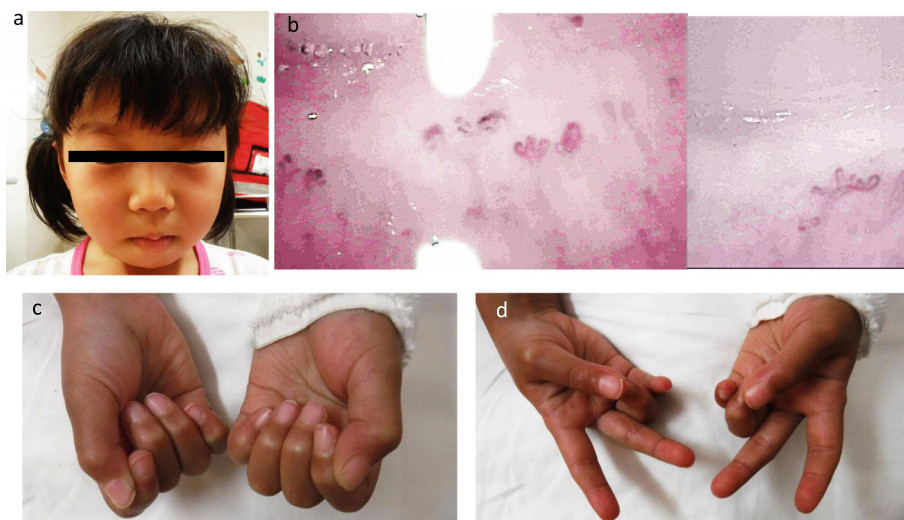
age of 2. The skin abnormality became more obvious, and a skin biopsy was performed from the left dorsal pedis at a previous institution when she was 5 years old. It revealed a fibrous thickening of the dermis, relative entrapment of an eccrine sweat glands, and thickened collagenous fiber (Fig. 1). Based on the findings, she was referred to our hospital. She presented characteristic appearance with mask-like or mouse-facies as taut facial skin, loss of wrinkles and skin folds, puffy fingers with Raynaud's phenomenon, and skin thickening of distal extremities beyond the elbows and knees (18/51 of the modified Rodnan total skin thickness score: mRSS) (Fig. 2) [11]. Grossly visible capillary hemorrhage on nail fold and severe abnormal capillaroscopy findings including bleeding, giant loop and disappearance of capillary consistent with the late phase in SSc. Contractures in the ankle and proximal interphalangeal joints resulted in gait disturbance and finger motion difficulty, respectively. There were neither abnormal neurological findings nor evidence suggesting myositis from information such as clinical muscle weakness, muscle derived enzyme, and muscle Magnetic Resonance Imaging at baseline intensive examination. Chest high-resolution computed tomography (HRCT) demonstrated patchy areas of ill-defined air-space opacity and consolidation predominantly involving the posterior basilar aspects of the lower lobes presenting with interstitial lung disease, although she had no symptoms suggesting respiratory abnormality, and no obvious finding could be detected by plain chest radiography (Fig. 3). Serum KL-6 level was 197 U/mL and was within the normal range. No abnormal findings were detected by electrocardiography or echocardiography. She manifested neither heartburn nor dysphagia, and findings of gastroesophageal reflux disease were not identified by esophago-gastroduodenoscopy. Esophageal dilatation and/or dysmotility was not indicated by the upper gastrointestinal series. Blood examination showed positive ANA (nucleolar and homogeneous nuclear staining at a serum dilution of 1:160 by indirect immunofluorescence) (Fig. 4). The commercially available SSc-related autoantibodies, including anti-topoisomerase I (Scl-70), anticentromere, and



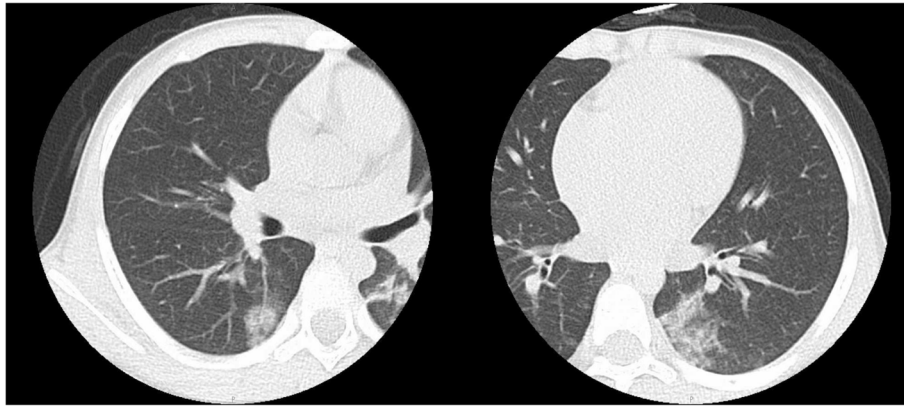
**Fig. 1** Histopathology findings in skin biopsy from the left dorsal pedis (low (left) and high (right) magnification); fibrous thickening of the dermis and relative entrapment of an eccrine sweat glands were observed. There were no pathological findings of vasculitis or vascular obstruction

anti-U1RNP, were not detected (Table 1). We then conducted an RNA immunoprecipitation assay and immunoprecipitation-immunoblot assay as previously described [12, 13]. The patient's serum immunoprecipitated ribosomal RNAs and a 7 – 2 RNA that was consistent with the RNA component precipitated by a reference anti-Th/To-positive serum (Fig. 5). In addition, the immunoprecipitation-immunoblot assay probed with anti-hPOP1 and anti-PM-Scl-100 antibodies revealed that the patient's serum contained both anti-Th/To and anti-PM-

Scl antibodies (Table 1). The patient was diagnosed with diffuse cutaneous SSc, based on the Pediatric Rheumatology European Society/American College of Rheumatology/European League Against Rheumatism Provisional Classification Criteria for Juvenile Systemic Sclerosis [14]. She was treated with 2 courses of methylprednisolone pulse therapy (30 mg/kg/day for 3 days each course) followed by 10 mg/day of oral prednisolone (PSL) (Fig. 6). Subsequently, 6 courses of monthly intravenous cyclophosphamide (IVCY, 500 mg/m<sup>2</sup> each course) therapy



**Fig. 2** Clinical features of the case patient. **a** Facial features at the time of admission; Shiny skin on the face. Face dimples previously could not be identified. **b** Nail fold capillaroscopy: severe abnormal capillaroscopy findings including bleeding, giant loop and disappearance of capillary consistent with the late phase in SSc. **c, d** Patient's hands at the time of admission; she had puffy fingers and induration of the skin proximal to the metacarpophalangeal joints, the difficulty of grasping hands

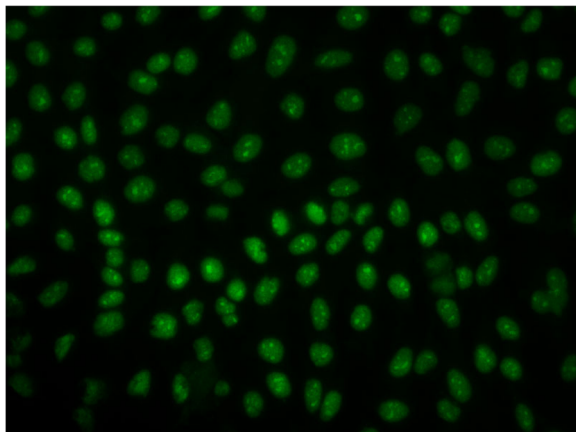


**Fig. 3** Chest high-resolution computed tomography (HRCT) scanning on admission. HRCT demonstrated patchy areas of ill-defined air-space opacity and consolidation predominantly involving the posterior basilar aspects of the lower lobes presenting with interstitial lung disease

were administered. In the second course of IVCY, her skin thickening improved and the mRSS was 4/51. Just before the third course of IVCY, the interstitial lesions at the basal lung field were not identifiable on follow-up HRCT, and joint contracture also improved. After completing 6 courses of IVCY without major adverse events, she was maintained with 25 mg/day of azathioprine and PSL. Her PSL dose was reduced from 10 mg/day to 3 mg/day during 7 months of the time course.

### Discussion

In this report, we describe a case of early childhood-onset SS. Particularly notable findings were the simultaneous identification of SSc-related anti-Th/To and anti-PM-Scl autoantibodies, rare anti-nucleolar autoantibodies. ANA seropositivity in three large pediatric SSc series was 78–97%, which is lower in children than in adults [6, 8, 9]. The predominant ANA patterns were

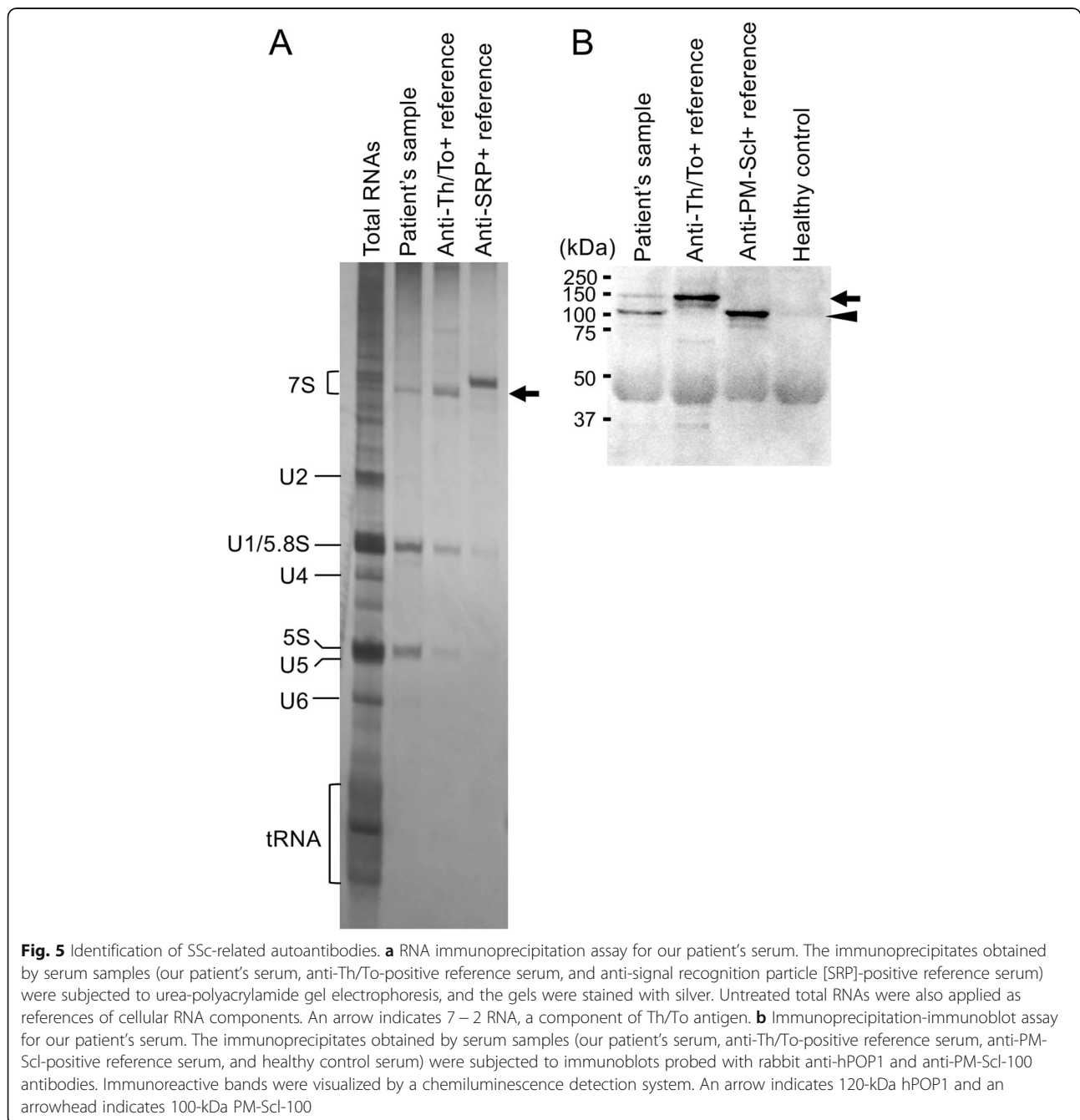


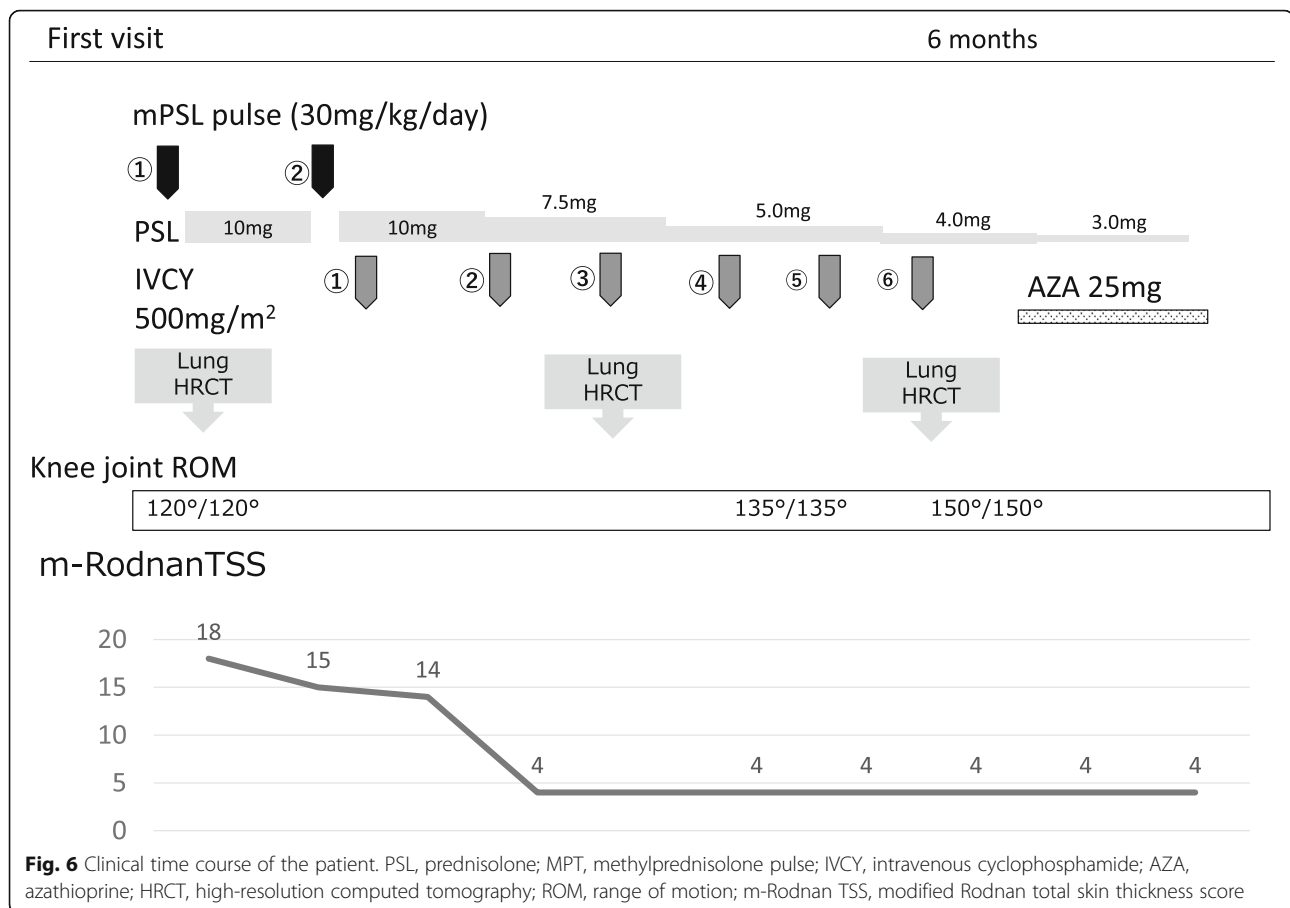
**Fig. 4** Anti-nuclear antibody was detected by indirect immunofluorescence. Nucleolar and homogeneous nuclear staining was identified at a serum dilution of 1:160

speckled and nucleolar staining. The pathogenesis of this disorder is not fully understood, but growing evidence suggests that T cells, B cells, and SSc-related autoantibodies participate in the disease process [15, 16]. It has been reported that over 85% of SSc patients have SSc-related autoantibodies, and that their detection is useful in diagnosis and disease subtyping [17, 18]. In adult-onset SSc, anti-topoisomerase I, anti-centromere, and anti-RNA polymerase III are the most prevalent autoantibodies [18]. Anti-topoisomerase I is associated with dcSSc and ILD, and is the most common autoantibody in childhood-onset SSc patients (28–34%) [6, 8, 9]. Anti-RNA polymerase III is associated with dcSSc and the greatest risk for developing scleroderma renal crisis [19], and is rarely found in juvenile-onset SSc. Patients with juvenile-onset SSc more frequently had an overlap syndrome of lcSSc and myositis and showed a higher prevalence of autoantibodies associated with sclerodermatomyositis compared with adult-onset SSc, that is, anti-PM-Scl (14% vs. 3%;  $p < 0.0001$ ) and anti-U1RNP antibodies (16% vs. 7% in adults;  $p < 0.0001$ ) [6]. Anti-PM-Scl antibody predominantly represents nucleolar staining by indirect immunofluorescence, often with a moderately high ANA titer [20]. In a large cohort of patients with anti-PM-Scl antibody, ILD was identified in 13% of patients with this antibody alone, and in 29% of patients with this and other SSc-related autoantibodies, including anticentromere, anti-topoisomerase I, and/or anti-RNA polymerase III [21]. Anti-Th/To antibody is another anti-nucleolar antibody and occurs in less than 5% of SSc patients in adults, but not in children [6]. Almost all patients with anti-Th/To antibody have lcSSc and are associated with either interstitial lung lesions (ILD) (45%) or pulmonary arterial hypertension (25%), within adult patients with lcSSc [22]. In a Japanese report of diffuse cutaneous SSc with anti-Th/To antibody, all three patients presented ILD and coexistence of anti-

**Table 1** SSc-related autoantibodies

SSc-related autoantibodies	Measurement methods	Present Case
Antinuclear antibodies (ANA)	Indirect immunofluorescence	1:160 nucleolar and homogeneous nuclear
Anti-topoisomerase I (anti-Scl70)	Chemiluminescent enzyme immunoassay (commercially available)	negative
Anticentromere	Enzyme-linked immunosorbent assay (commercially available)	negative
Anti-RNA polymerase III	Enzyme-linked immunosorbent assay (commercially available)	negative
Anti-U1RNP	Chemiluminescent enzyme immunoassay (commercially available)	negative
Anti-Th/To	Immunoprecipitation-immunoblot assay	positive
Anti-PM-Scl	Immunoprecipitation-immunoblot assay	positive





topoisomerase I antibody [23]. This is the first case report of juvenile SSc with two rare anti-nucleolar specificities, including anti-PM-Scl and anti-Th/To antibodies. Notably, patients with childhood-onset SSc had a significantly higher positivity for two or more SSc-related autoantibodies (8 % vs. 1.5 %;  $p < 0.005$ ) than adult-onset patients [6]. Our patient had dcSSc with prominent joint contractures was apparently inconsistent with the clinical features of anti-PM-Scl or anti-Th/To antibodies reported in adults. Clinical characteristics associated with SSc-related antibodies are derived from studies almost exclusively involving adult-onset SSc patients, which might differ between juvenile and adult patients with SSc.

## Conclusions

We experienced the first known case of juvenile SSc with anti-PM-Scl and anti-Th/To antibodies. ILD was identified as a typical feature of the autoantibodies; however, diffuse cutaneous SSc and joint contraction were uncharacteristically associated. The case revealed unexpected clinical findings though the existence of SSc-related autoantibodies basically aided in determining of

possible organ involvement and estimation of the patient's outcome.

## Abbreviations

SSc: Systemic sclerosis; dcSSc: Diffuse cutaneous SSc; ILD: Interstitial lung disease; mRSS: Modified Rodnan total skin thickness score; ANA: Anti-nuclear antibody; HRCT: Chest high resolution computed tomographic scanning; PSL: Prednisolone; IVCY: Intravenous cyclophosphamide

## Acknowledgements

We thank the patient and her family for their consent to participate in this study. We also would like to thank Editage (<http://www.editage.com>) for English language editing.

## Authors' contributions

Riki Tanaka, Takako Miyamae, Yumi Tani, Yoichiro Kaburaki, and Yasushi Kawaguchi carried out the diagnosis and management of the patient and drafted the manuscript. Manao Kinoshita performed a skin biopsy. Yuka Okazaki and Masataka Kuwana analyzed and interpreted the results of an RNA immunoprecipitation assay and immunoprecipitation-immunoblot assay. Takako Miyamae and Masataka Kuwana helped draft the manuscript. Harigai Masayoshi and Satoru Nagata contributed to the final version of the manuscript. All authors have read and approved the final manuscript.

## Funding

None.

## Declarations

### Ethics approval and consent to participate

Oral informed assent and written informed consent were obtained from the patient.

### Consent for publication

Oral informed assent and written informed consent were obtained from the patient.

### Availability of data and materials

The datasets generated and/or analysed during the current study are not publicly available due [REASON WHY DATA ARE NOT PUBLIC] but are available from the corresponding author on reasonable request.

### Competing interests

The authors declare that they have no competing interests.

### Author details

<sup>1</sup>Department of Pediatrics, Tokyo Women's Medical University, Tokyo, Japan, 8-1 Kawada-Cho, Shinjuku- Ku, 162-8666 Tokyo, Japan. <sup>2</sup>Institute of Rheumatology, Tokyo Women's Medical University, Tokyo, Japan, 8-1 Kawada-Cho, Shinjuku- Ku, 162-8666 Tokyo, Japan. <sup>3</sup>Department of Dermatology, Faculty of Medicine, University of Yamanashi, Yamanashi, Japan, Shimokoto, Chuo, 1110, 409-3898 Yamanashi, Japan. <sup>4</sup>Department of Allergy and Rheumatology, Nippon Medical School, 1-1-5 Sendagi, Bunkyo-Ku, 113- 8602 Tokyo, Japan.

Received: 1 July 2020 Accepted: 5 March 2021

Published online: 20 March 2021

## References

- Gabrielli A, Avvedimento EV, Krieg T. Scleroderma. *N Engl J Med*. 2009;360:1989–2003.
- Hedrich CM, Fiebig B, Hahn G, Suttorp M, Gahr M. Presentations and treatment of childhood scleroderma: localized scleroderma, eosinophilic fasciitis, systemic sclerosis, and graft-versus-host disease. *Clin Pediatr (Phila)*. 2011;50:604–14.
- Arias-Nunez MC, Llorca J, Vazquez-Rodriguez TR, Gomez-Acebo I, Miranda-Filloo JA, Martin J, et al. Systemic sclerosis in northwestern Spain: a 19-year epidemiologic study. *Med (Baltim)*. 2008;87:272–80.
- Lawrence RC, Helmick CG, Arnett FC, Deyo RA, Felson DT, Giannini EH, et al. Estimates of the prevalence of arthritis and selected musculoskeletal disorders in the United States. *Arthritis Rheum*. 1998;41:778–99.
- Mayes MD, Lacey JV Jr, Beebe-Dimmer J, Gillespie BW, Cooper B, Laing TJ, et al. Prevalence, incidence, survival, and disease characteristics of systemic sclerosis in a large US population. *Arthritis Rheum*. 2003;48:2246–55.
- Scalapino K, Arkachaisri T, Lucas M, Fertig N, Helfrich DJ, Londino AV Jr, et al. Childhood onset systemic sclerosis: classification, clinical and serologic features, and survival in comparison with adult onset disease. *J Rheumatol*. 2006;33:1004–13.
- Black CM. Scleroderma in children. *Adv Exp Med Biol*. 1999;455:35–48.
- Foeldvari I, Klotsche J, Torok KS, Kasapcopur O, Adrovic A, Stanevicha V, et al. Are diffuse and limited juvenile systemic sclerosis different in clinical presentation? Clinical characteristics of a juvenile systemic sclerosis cohort. *J Scleroderma Relat Disord*. 2018;4:49–61.
- Martini G, Foeldvari I, Russo R, Cuttica R, Eberhard A, Ravelli A, et al. Juvenile Scleroderma Working Group of the Pediatric Rheumatology European Society. Systemic sclerosis in childhood: clinical and immunologic features of 153 patients in an international database. *Arthritis Rheum*. 2006;54:3971–8.
- Sampaio-Barros PD, Bortoluzzo AB, Del Rio AP, Luppino-Assad AP, Andrade DC, Marques-Neto JF. Clinical and laboratory profile of juvenile-onset systemic sclerosis in a Brazilian cohort. *J Scleroderma Rel Disord*. 2019;4:43–8.
- Clements PJ, Lachenbruch PA, Seibold JR, Zee B, Steen VD, Brennan P, et al. Skin thickness score in systemic sclerosis: an assessment of interobserver variability in 3 independent studies. *J Rheumatol*. 1993;20:1892–6.
- Forman MS, Nakamura M, Mimori T, Gelpi C, Hardin JA. Detection of antibodies to small nuclear ribonucleoproteins and small cytoplasmic ribonucleoproteins using unlabeled cell extracts. *Arthritis Rheum*. 1985;28:1356–61.
- Kang EH, Kuwana M, Okazaki Y, Lee EY, Lee YJ, Lee EB, et al. Comparison of radioimmunoprecipitation versus antigen-specific assays for identification of myositis specific autoantibodies in dermatomyositis patients. *Mod Rheumatol*. 2014;24:945–8.
- Zulian F, Woo P, Athreya BH, Laxer RM, Medsger TA Jr, Lehman TJ, et al. The PRES/ACR/EULAR provisional classification criteria for juvenile systemic sclerosis. *Arthritis Rheum*. 2007;57:203–12.
- Varga J, Abraham D. Systemic sclerosis: a prototypic multisystem fibrotic disorder. *J Clin Invest*. 2007;117:557–67.
- Sakkas LI, Bogdanos DP. Systemic sclerosis: new evidence reinforces the role of B cells. *Autoimmun Rev*. 2016;15:155–61.
- Nihtyanova SID. Autoantibodies as predictive tools in systemic sclerosis. *Nat Rev Rheumatol*. 2010;5:112–6.
- Liaskos C, Marou E, Simopoulou T, Barmakoudi M, Efthymiou G, Scheper T, et al. Disease-related Autoantibody Profile in Patients With Systemic Sclerosis. *Autoimmunity*. 2017;50:414–21.
- Hamaguchi Y, Kodera M, Matsushita T, Hasegawa M, Inaba Y, Usuda T, et al. Clinical and immunologic predictors of scleroderma renal crisis in Japanese systemic sclerosis patients with anti-RNA polymerase III autoantibodies. *Arthritis Rheumatol*. 2015;67:1045–52.
- Domsic RT, Medsger TA. Autoantibodies and Their Role in Scleroderma Clinical Care. *Curr Treat Options in Rheum*. 2016;2:239–51.
- D'Aoust J, Hudson M, Tatibouet S, Wick J, Canadian Scleroderma Research Group, Mahler M, Baron M, Fritzler MJ. Clinical and serologic correlates of anti-PM/Scl antibodies in systemic sclerosis: a multicenter study of 763 patients. *Arthritis Rheumatol*. 2014;66:1608–15.
- Mitri GM, Lucas M, Fertig N, Steen VD, Medsger TA Jr. A comparison between anti-Th/To- and anticentromere antibody-positive systemic sclerosis patients with limited cutaneous involvement. *Arthritis Rheum*. 2003;48:203–9.
- Kuwana M, Kimura K, Hirakata M, Kawakame Y, Ikeada Y. Differences in autoantibody response to Th/To between systemic sclerosis and other autoimmune diseases. *Ann Rheum Dis*. 2002;61:842–6.

## Publisher's Note

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

**Ready to submit your research? Choose BMC and benefit from:**

- fast, convenient online submission
- thorough peer review by experienced researchers in your field
- rapid publication on acceptance
- support for research data, including large and complex data types
- gold Open Access which fosters wider collaboration and increased citations
- maximum visibility for your research: over 100M website views per year

**At BMC, research is always in progress.**

Learn more [biomedcentral.com/submissions](https://biomedcentral.com/submissions)

