Anti-cyclic Citrullinated Peptide Antibody-positive Girl with Chronic Polyarthritis Later Diagnosed with Juvenile Systemic Lupus Erythematosus: A Case Report

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Background: Arthritis is one of the earliest symptoms of juvenile systemic lupus erythematosus (SLE) but is unusual in cases presenting with chronic arthritis or deforming/erosive arthritis. Overlap of juvenile idiopathic arthritis (JIA) and juvenile SLE is a rare clinical condition known as "rhupus" syndrome. The clinical and serological characteristics of rhupus syndrome in children remain to be established. In addition, no studies regarding anti-cyclic citrullinated peptide (CCP) antibody in juvenile SLE or juvenile rhupus syndrome have been reported.
Case Report: A 12-year-old girl suffered from polyarthralgia lasting for one week. She was tentatively diagnosed with polyarticular JIA because of her symptom of chronic arthritis and a positive result for anti-CCP antibody. After six months of follow-up for JIA, she presented with a fever, malar rash, and worsening of arthralgia. Laboratory examinations revealed hypocomplementemia and a positive result for anti-double-stranded DNA antibody. She was diagnosed with juvenile SLE.
Conclusions: It is important to note that patients with chronic arthritis, as well as those with anti-CCP antibody-positive polyarthritis, should be carefully followed for their clinical and serological condition, considering the possibility of them developing juvenile SLE.

Key words: SLE, anti-CCP antibody, arthritis, rhupus syndrome, children

INTRODUCTION

Systemic lupus erythematosus (SLE) is a multisystem autoimmune rheumatic disorder characterized by both clinical and immunological abnormalities. Articular symptoms are the most common clinical manifestations, occurring in approximately 90% of SLE patients during course of the disease [1–3]. Arthritis in juvenile SLE is also one of the earliest symptoms but is characteristically short in duration and can be transient, migratory, reversible, and usually nonerosive [1, 4].

Anti-cyclic citrullinated peptide (CCP) antibody is a serological marker used in the diagnosis and prognostication of rheumatoid arthritis (RA) [5]. A previous study showed that anti-CCP antibody was positive in 20.6% of patients with juvenile idiopathic arthritis (JIA) but negative in those with juvenile SLE and healthy controls [6].

Overlap of RA and SLE is a rare clinical condition that has been described as "rhupus" syndrome. It is defined as meeting the criteria of both RA and SLE and has an estimated prevalence rate of 0.09% in adults [7]. There have been few reports of rhupus syndrome in children, so the clinical characteristics of the overlap of JIA and juvenile SLE remain to be established.

We herein report a rare case of a 12-year-old girl with anti-CCP antibody-positive polyarticular arthritis who subsequently developed SLE 6 months after the tentative diagnosis of JIA was made. Informed consent was obtained from the parents of patient and assent was obtained from children considered old enough (> 9 years old).

CASE REPORT

A 12-year-old girl with bronchial asthma, atopic dermatitis, and obesity visited our hospital because of polyarthralgia in the bilateral knees, hips, elbows, and proximal interphalangeal joints, lasting for 1 week. She also presented with difficulty walking and limitation of joint movement in those joints.

A laboratory investigation at her first hospital visit revealed a normal complete blood count but elevated values of erythrocyte sedimentation rate (ESR; 47 mm/h), C-reactive protein (CRP; 0.836 mg/dL), and matrix metalloproteinase 3 (MMP-3; 66.2 ng/mL). Although rheumatoid factor, anti-CCP antibody (1,270 U/mL), antinuclear antibody (Homogeneous pattern 1/160; Speckled pattern 1/160), and anti-double-stranded DNA (ds-DNA) antibody levels were elevated, other autoantibodies, such as anti-Sm and anti-RNP, were negative, and serum complement levels were normal (Table 1).

Magnetic resonance imaging (MRI) of both knees and elbows revealed chronic inflammation with syno-

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Table 1 Blood examination at the time of JIA diagnosis and SLE diagnosis.

	at JIA diagnosis	at SLE diagnosis
White blood cell count	8,700/μL	4,000/μL
Neutrophils	65.9%	71.0%
Lymphocytes	22.6%	21.0%
Monocytes	9.6%	6.0%
Red blood cell count	479 × 10^4/μL	464 × 10^4/μL
Hemoglobin	13.1 g/dL	12.1 g/dL
Hematocrit	39.4%	36.9%
Platelets	380 × 10^3/μL	363 × 10^3/μL
Erythrocyte sedimentation rate	47 mm/hr	64 mm/hr
C-reactive protein	0.836 mg/dL	1.046 mg/dL
Matrix metalloproteinase 3	66.2 ng/mL	408 ng/mL
C3	155 mg/dL	84 mg/dL
C4	29 mg/dL	7 mg/dL
CH50	46.8 U/mL	18.6 U/mL
Antinuclear antibody	1/160	1/320
(Pattern)	Homogeneous 1/160 Speckled 1/160	Homogeneous 1/320 Speckled 1/320
Anti-ds-DNA antibody	39 IU/mL	111 IU/mL
Rheumatoid factor	29 IU/mL	28 IU/mL
Anti-CCP antibody	1,270 U/mL	1,910 U/mL
Anti-Sm antibody	(-)	(+)
Anti-RNP antibody	(-)	(+)
Anti-SS-A/Ro antibody	(+)	(+)
Anti-SS-B/La antibody	(-)	(-)

CCP, cyclic citrullinated peptide; ds-DNA, double-stranded DNA; JIA, juvenile idiopathic arthritis; SLE, systemic lupus erythematosus.

vial thickening along with Baker's cyst in the left knee, suggesting chronic arthritis (Fig. 1).

She was tentatively diagnosed with polyarticular JIA according to the Japanese pediatric guideline for diagnosis and treatment for juvenile idiopathic arthritis, that is, the presence of more than six weeks continuous arthritis from unknown origin excluding infectious diseases, the other autoimmune diseases, malignant diseases, and, so on. At this time, we could not diagnose the patient with SLE because the patient met only three criteria of juvenile SLE such as arthralgia, positive results of anti-ds-DNA antibody and antinuclear antibody. For these reasons, we treated with methotrexate (MTX) 6 mg once weekly orally (Fig. 2). She was regularly followed up at one-month intervals. As her arthralgia was not adequately improved and her MMP-3 levels remained elevated, the MTX dose was increased to 8 mg once weekly. From these observations, we were considering about treating with anti-TNF inhibitor at that time, while we could not diagnose the patient with SLE because the patient did not meet the criteria of juvenile SLE.

At the six-month follow-up of JIA, but also at one week before the diagnosis of SLE, she presented with a fever, malar rash, and worsening of arthralgia in both knees. At that time, while the other SLE symptoms were not confirmed, laboratory examinations revealed elevated values of ESR 64 mm/h, CRP 1.046 mg/dL, and MMP-3 408 ng/mL; decreased serum complement levels (CH50 18.6 U/mL, C3 84 U/mL, C4 7 U/mL); positive results for anti-ds-DNA antibody, anti-Sm antibody, anti-RNP antibody, and anti-SS-A/Ro antibody (Table 1). She also had mild proteinuria, and a renal biopsy revealed class II lupus nephritis based on the criteria proposed by the International Society of Nephrology/Renal Pathology Society (ISN/IRPS) [8].

Cardiac ultrasonography, head and salivary MRI, chest computed tomography, and an ophthalmological examination showed no signs of complications, such as pericarditis, pneumonitis, sialadenitis, retinal vasculitis, and uveitis. She was diagnosed with juvenile SLE according to the 1997 Update of the 1982 American College of Rheumatology revised criteria for the classification of SLE [9].

Initial treatment consisted of 2 courses of intravenous methylprednisolone pulse therapy (1,000 mg/day, consecutive 3 days, 1-week interval), followed by oral prednisolone 40 mg/day, according to Japanese pediatric guideline for the treatment of SLE. While MTX was discontinued due to the diagnosis of SLE, hydroxychloroquine was administered at 200–400 mg on alternate days (Fig. 2). After four months of follow-up from the diagnosis of SLE, the serum complement levels, ESR, and anti-ds-DNA antibodies were normalized, and eventually she achieved remission.

Prednisolone was gradually reduced to low dose.

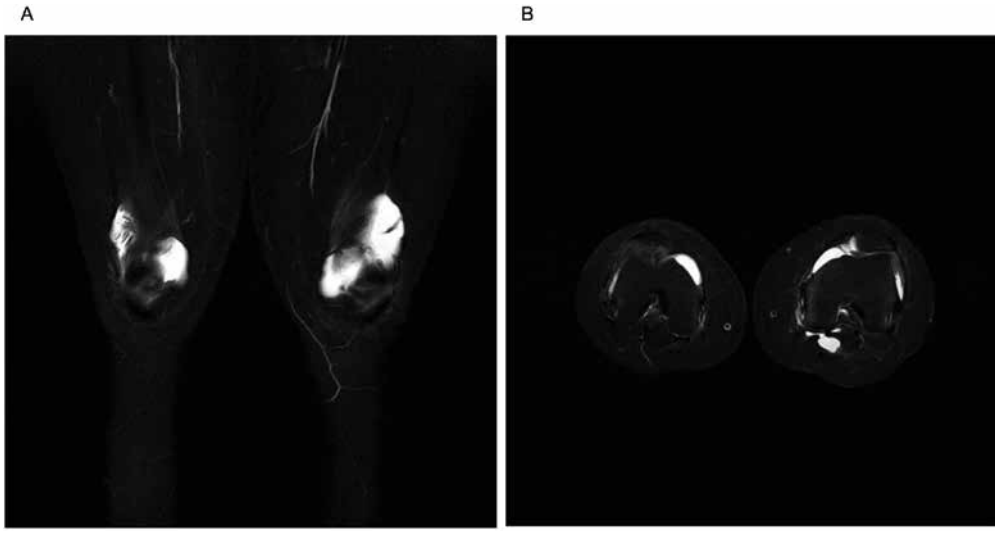

Fig. 1 (A) MRI of both knees demonstrated chronic inflammation with synovial thickening. (B) MRI of left knee revealed Baker's cyst.

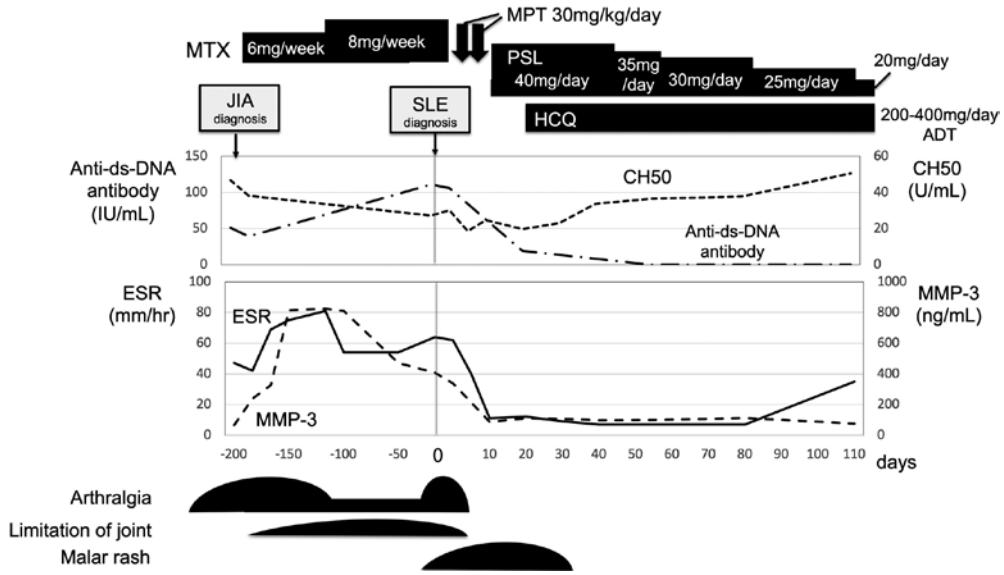

Fig. 2 The clinical course, laboratory findings, and treatment of our case. After six months of follow-up for JIA, she presented with a fever, malar rash, and worsening of arthralgia. Laboratory examinations revealed hypocomplementemia and positivity for anti-double-stranded DNA antibody. She was diagnosed with juvenile SLE and started two courses of intravenous methylprednisolone pulse therapy, followed by oral prednisolone and hydroxychloroquine. Her joint pain and limitation of the joint range of motion were rapidly improved. After four months of follow-up after the diagnosis of SLE, the serum complement levels, ESR, and anti-ds-DNA antibodies were normalized, and eventually she achieved remission. ADT, alternate-day treatment; ds-DNA, double-stranded DNA; ESR, erythrocyte sedimentation rate; HCQ, hydroxychloroquine; JIA, juvenile idiopathic arthritis; MMP-3, matrix metalloproteinase 3; MPT, methylprednisolone pulse therapy; MTX, methotrexate; PSL, prednisolone; SLE, systemic lupus erythematosus.

MRI of the bilateral knee joints showed an improvement in inflammation. However, although the clinical symptoms were improved by treatment, the RF, anti-CCP antibody, and MMP-3 levels remain elevated, so additional treatment will need to be considered, depending on the course of the disease.

DISCUSSION

Our case met the SLE criteria at six months after the first manifestation of joint involvement and the tentative diagnosis of polyarticular JIA with positivity for anti-CCP antibody. She had chronic arthritis but no erosive or deforming arthropathy. She might be considered to have rhupus syndrome because she met the criteria of both JIA and SLE. Of note, anti-Sm antibody and anti-RNP antibody converted to be positive in a short interval from diagnosis of JIA. To our knowledge, this is the first case report wherein a polyarticular arthritis patient with anti-CCP antibody subsequently developed juvenile SLE in a relatively short interval between the diagnoses of JIA and SLE.

In this case, confirming chronic arthritis, defined as

synovitis lasting at least six weeks, led to the tentative diagnosis of JIA. Chronic arthritis is an uncommon condition in juvenile SLE [10]. Cavalcante *et al.* reported that the prevalence of chronic arthritis in juvenile SLE was 2.6%. In addition, chronic arthritis was the initial manifestation in those SLE patients, and the median duration of chronic arthritis was 11 months (range 2–15 months) [11]. Another study showed that 32 juvenile SLE patients with chronic arthritis presented with monoarthritis in 4 (12.5%), oligoarthritis in 9 (28.1%), and polyarthritis in 19 (59.4%) [10]. Regarding the differences between child and adult SLE patients with chronic arthritis, chronic arthritis in juvenile SLE patients had an earlier onset, higher incidence of polyarthritis, and more joints with arthritis or limitation than did that in adult patients [12]. Our case was consistent with these observations, with its initial manifestation of polyarthritis with joint limitation.

To our knowledge, there has been no study concerning positivity for anti-CCP antibody in juvenile SLE patients. A previous observational study showed that anti-CCP antibodies were detected in 357 (30.7%) of 1,162 rheumatic disease patients; anti-CCP antibodies were detected in 292/417 patients with RA (70.0%), 5/31 patients with SLE (16.1%), 2/25 patients with mixed connective tissue disease (8.0%), and 7/44 patients with JIA (15.9%) [13]. Focusing on SLE patients, another study showed that anti-CCP antibody in SLE was detected in 42.1% of patients with arthritis and in 5.6% of those without arthritis and tended to be associated with hand polyarthritis [14]. Several studies have also suggested that anti-CCP antibodies in SLE were significantly associated with deforming/erosive arthritis [14–17]. Budhram *et al.* showed that the sensitivity and specificity of anti-CCP antibody for erosive arthritis in SLE were 47.8% and 91.8%, respectively [18]. Although the findings in our case were consistent with these findings, further studies will be required to clarify the characteristics of juvenile SLE with positivity for anti-CCP antibody.

This case might be one of rhupus syndrome, with overlapping diagnoses of JIA and SLE. There have been few reports of rhupus syndrome in children. Ziaee *et al.* reviewed previous reports of rhupus syndrome in children and found that the patients with both JIA and SLE had joint erosion in 45% and polyarthritis in 70%, and the SLE diagnosis was delayed by a mean 50.1 months (range 9–120 months) [4]. A previous study in adults showed that rhupus syndrome patients were diagnosed with the onset of RA (83.9%) and developed SLE within 7.8 years (median) [19]. The same study also showed that rhupus patients had a lower incidence of malar rash, hemolytic anemia, and renal and neurological involvement than SLE patients. Furthermore, rhupus patients had mild SLE disease activity, an extremely low rate of visceral organ involvement, and rarely had severe renal disorders, such as nephrotic syndrome and renal insufficiency [19]. Collectively, a slow progressive disease course of rhupus syndrome has been indicated, in contrast to our case's relatively short interval of developing SLE, suggesting that our case's diagnosis was more compatible with SLE.

In conclusion, we reported a rare case of juvenile SLE that developed after a diagnosis of anti-CCP antibody-positive polyarthritis had been made. Our findings suggested that anti-CCP antibody in juvenile SLE may play an important role in the pathogenesis of juvenile rhupus syndrome. Furthermore, of note, patients with chronic arthritis as well as those with anti-CCP antibody-positive polyarthritis should be carefully followed for their SLE symptoms in consideration of the possibility of developing juvenile SLE. Specifically, it is important to monitor anti-ds-DNA antibody titer, seropositive conversion of anti-Sm antibody and/or anti-RNP antibody even in a short duration. Further studies will be needed to elucidate the pathogenesis of juvenile rhupus syndrome and potential role of anti-CCP antibody in children.

DISCLOSURE STATEMENT

The authors declare that no financial or other conflicts of interest exist in relation to the contents of this article.

AUTHOR CONTRIBUTION

The authors confirm contribution to the paper as follows: study conception and design: Y.K.; data collection: A.T., S.O., T.S., H.T., K.H.; interpretation of results: Y.K., M.K.; draft manuscript preparation: Y.K., A.T., M.K.. All authors reviewed the results and approved the final version of the manuscript.

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