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ORIGINAL ARTICLE

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Anticyclic citrullinated peptide antibodies in patients with mixed connective tissue disease

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Abstract The clinical significance of anticyclic citrullinated peptide (CCP) antibodies in patients with mixed connective tissue disease (MCTD) was assessed. Altogether, 86 sera from MCTD patients, 96 from rheumatoid arthritis (RA) patients, 42 from systemic lupus erythematosus (SLE) patients, 23 from systemic sclerosis (SSc) patients, 21 from poymyositis/dermatomyositis (PM/DM) patients, and 17 from those with Sjögren's syndrome (SjS) were tested for anti-CCP antibodies using an enzyme-lined immunosorbent assay. Among the 96 RA patients, anti-CCP antibodies were detected in 85%, with the frequency being significantly higher than in MCTD, SLE, SSc, PM/DM, and SjS patients (9%, 14%, 13%, 14%, and 18%, respectively; $P < 0.001$). Among eight MCTD patients who fulfilled the diagnostic criteria for RA, only 50% had anti-CCP antibodies, and the prevalence was significantly lower than for all RA patients ($p < 0.01$). All eight patients who fulfilled the criteria for RA had overlap of SLE and SSc, except one patient, whereas the four anti-CCP-positive patients who did not fulfill the criteria for RA had SjS without overlapping features of SLE and SSc; moreover, most of their antibody titers were low. These results suggested that anti-CCP antibodies are associated with RA in MCTD patients, but careful diagnosis of RA is required if patients with low titers of anti-CCP antibodies lack overlapping SLE and SSc.

Key words Autoantibody · Cyclic citrullinated peptide (CCP) · Mixed connective tissue disease (MCTD) · Rheumatoid arthritis (RA)

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Introduction

Mixed connective tissue disease (MCTD) was first reported by Sharp et al. as a distinct clinical entity with overlapping features of systemic lupus erythematosus (SLE), scleroderma (SSc), and polymyositis (PM), as well as high titers of antibodies reactive with U1 ribonucleoprotein (U1 RNP).[1–3] They reported that almost all of these patients have arthralgia, and 60%–70% have arthritis that is nonerosive and nondeforming.[1] However, subsequent studies on the clinical and radiographic manifestations of MCTD have shown that more than 30% of patients have developed erosive arthritis and joints like those seen in patients with rheumatoid arthritis (RA).[4–9] Therefore, it is widely accepted that RA is also part of the disease spectrum of this overlapping syndrome.[4–9]

Recently, antibodies to cyclic citrullinated peptide (CCP) were reported as a novel serological marker for RA, with higher specificity than rheumatoid factor (RF).[10–12] Although recent studies on anti-CCP antibodies have clearly shown their usefulness for the early diagnosis of RA and evaluation of the prognosis,[10–14] the clinical significance of these antibodies in regard to MCTD (which is often accompanied by RA) has not been well defined. Therefore, we investigated whether anti-CCP antibodies were clinically useful for detecting the RA-like syndrome in patients with MCTD.

Materials and methods

Serum samples

Altogether, 86 serum samples from MCTD patients, 96 from RA patients, 42 from SLE patients, 23 from SSc patients, 21 from PM/dermatomyositis (DM) patients, and 17 from Sjögren's syndrome (SjS) patients were randomly selected from the serum bank at Juntendo University Hospital and were tested for anti-CCP antibodies by enzyme-linked immunosorbent assay (ELISA). MCTD was

diagnosed according to the criteria proposed by the Special Research Committee for MCTD of the Japanese Ministry of Health and Welfare (Kasukawa criteria).[15] All of the patients with SLE, SSc, and RA met the diagnostic criteria proposed by the American College of Rheumatology.[16–18] The PM/DM patients fit the criteria of Bohan et al.,[19] and the SjS patients were diagnosed in accordance with the criteria proposed by the European Community.[20]

Standard sera containing autoantibodies to nuclear antigens (including U1 RNP, Sm, SS-A/Ro, and SSB/La) were kindly donated by Dr. Eng M. Tan, M.D. (Autoimmune Research Center, The Scripps Research Institute, La Jolla, CA, USA) and were used for double immunodiffusion (DID) assays.

DID assay

The DID assays were conducted on plates containing 0.4% agarose (Sea Kem, Rockland, ME, USA) and 0.01% sodium azide in phosphate-buffered saline (PBS) (0.01 M phosphate buffer, 0.15 M NaCl, pH 7.4) to detect antibodies to U1 RNP, Sm, SS-A/Ro, and SS-B/La.[21] Precipitation reactions were allowed to develop for 48 h at room temperature.

Anti-CCP ELISA

Anti-CCP antibodies were detected by a second-generation anti-CCP ELISA system, which was originally reported by van Venrooij et al.[12] (DIASTAT Anti-CCP ELISA test purchased from Axis-Shield, Dundee, UK), and the assay was conducted according to the manufacturer's instructions. Serum samples of 100 µl (diluted 1:100) were added to the wells and incubated at room temperature for 60 min. After samples were removed and wells were washed three times with a minimum of 200 µl diluted "wash buffer," 100 ml of "conjugate solution" was added to each well and incubated for 30 min at room temperature. After washing, 100 µl of "substrate solution" was added, and the optical density (OD) at 550 nm was measured.

The ELISA unit (absorbance ratio) was calculated as follows.

$$\text{Unit} = \frac{\text{samples or "control" absorbance value}}{\text{mean "reference control" absorbance value}}$$

The optimal cutoff value for the assay (4.5 U/ml) was determined from the receiver operating characteristic (ROC) curve using 549 sera from RA patients and 320 sera from normal subjects, as reported previously.[14]

Results

Anti-CCP antibodies in patients with various connective tissue diseases

Serum samples from patients with various connective tissue diseases, including MCTD, were tested for anti-CCP antibodies by ELISA (Fig. 1, Table 1). Of the 96 patients with RA, anti-CCP antibodies were detected in 85%, thus being significantly more common than in patients with the other connective tissue diseases, including MCTD, SLE, SSc, PM/DM, and SjS (9%, 14%, 13%, 14%, and 18%, respectively; all $P < 0.001$). Although 8 of 86 MCTD patients fulfilled the criteria for RA, only 50% of them had anti-CCP antibodies (Table 1), which was a significantly lower prevalence than among the RA patients ($P < 0.01$). Among patients with connective tissue diseases other than RA, the prevalence of anti-CCP antibodies was lowest in those with MCTD (9%) and highest in those with SjS (18%) (Table 1). When the anti-CCP antibody titers of these patients were assessed (Fig. 1), the titer was also significantly higher in RA patients

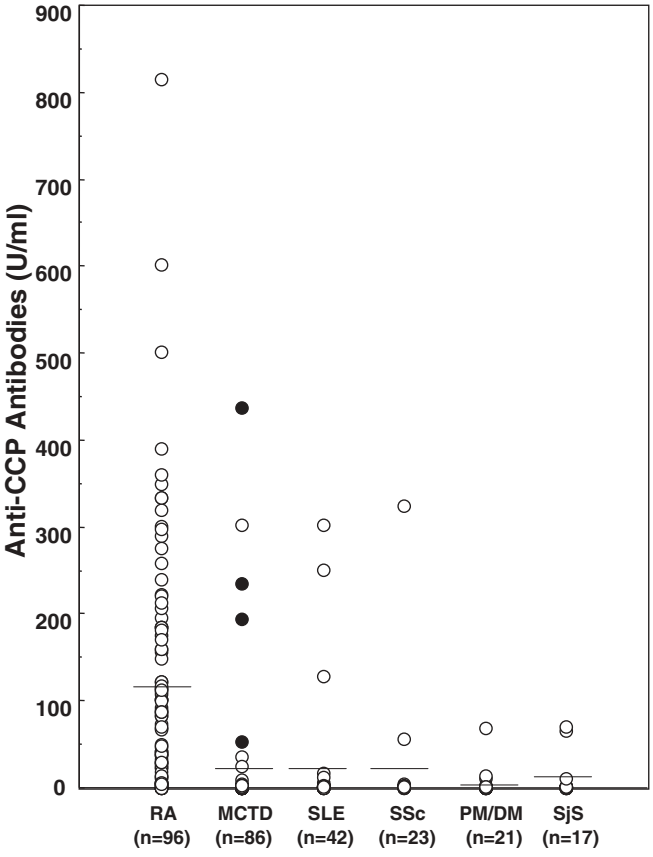

Fig. 1. Anticyclic citrullinated peptide (*CCP*) antibodies in various connective tissue diseases. Serum samples from connective tissue diseases including mixed connective tissue disease (*MCTD*) were tested for anti-CCP antibodies by enzyme-linked immunosorbent assay (ELISA). Of 96 patients with rheumatoid arthritis (*RA*), anti-CCP antibodies were detected in 85%, and the prevalence was significantly higher than in the other connective tissue diseases such as MCTD, systemic lupus erythematosus (*SLE*), scleroderma (*SSc*), poymyousitis/dermatomyositis (*PM/DM*), and Sjögren's syndrome (*SjS*) (9%, 14%, 13%, 14%, and 18%, respectively; $P < 0.0001$) (Table 1). The titer of anti-CCP antibodies was also significantly higher in RA (119.6 ± 140.6; *horizontal bars* indicate mean values) compared with other connective tissue diseases (MCTD 16.6 ± 66.2, SLE 18.4 ± 61.9, SSc 17.8 ± 67.7, PM/DM 5.3 ± 15.0, and SjS 9.5 ± 22.4; all $P < 0.001$). Although the prevalence of these antibodies was lowest in the presence of MCTD, all but one of the MCTD patients who had high anti-CCP titers had been diagnosed as having RA (*closed circles*)

Table 1. Frequency of anti-CCP antibodies in various connective tissue diseases

Disease	No. of patients	Frequency (%)
RA	96	85[a]
MCTD	86	9
MCTD with RA	8	50[b]
SLE	42	14
SSc	23	13
PM/DM	21	14
SjS	17	18

CCP, cyclic citrullinated peptide; RA, rheumatoid arthritis; MCTD, mixed connective tissue diseases; SLE, systemic lupus erythematosus; SSc, scleroderma; PM/DM, polymyositis/dermatomyositis; SjS, Sjögren's syndrome

[a] The frequency of anti-CCP antibodies in RA patients is significantly higher than in other connective tissue diseases ($P < 0.001$)

[b] The frequency in eight MCTD patients who fulfilled the criteria for RA is significantly lower than that in RA patients ($P < 0.01$)

(119.6 ± 140.6) than in patients with other connective tissue diseases (MCTD 16.6 ± +66.2, SLE 18.4 ± 61.9, SSc 17.8 ± 67.7, PM/DM 5.3 ± 15.0, SjS 9.5 ± 22.4; $P < 0.001$). Although the prevalence of these antibodies was lowest in MCTD patients, the MCTD patients who had high anti-CCP titers had been diagnosed as having RA (closed circles in Fig. 1) with one exception.

Clinical characteristics of MCTD patients with anti-CCP antibodies and MCTD patients with RA

Fifty percent of MCTD patients who fulfilled the diagnostic criteria for RA were negative for anti-CCP antibodies, so the clinical features associated with anti-CCP antibodies in MCTD patients were compared with the features of patients without such antibodies (Table 2). Although the number of patients with anti-CCP antibodies was small, features of RA, such as morning stiffness (100%), persistent arthritis

Table 2. Clinical characteristics of MCTD patients with anti-CCP antibodies

Clinical feature	Patients (%)	
	With anti-CCP Abs ($n = 8$)	Without anti-CCP Abs ($n = 78$)
Raynaud's phenomenon	100	100
Swollen fingers/hand	100	100
Joint involvement		
Morning stiffness	100*	8
Arthralgia	100	99
Arthritis	100	95
Persistent arthritis (>6 weeks)	63*	8
Symmetrical arthritis	63*	5
Deformity	50*	3
Erosion (bone radiography)	63*	5
Photosensitivity	0	11
Malar rush	0	14
Alopecia	13	6
Pleuritis	0	8
Pericarditis	13	5
Lymphadenopathy	50	33
CNS involvement	13	3
Proteinuria	38	51
Hemolytic anemia	13	3
Leukopenia	75	65
Thrombocytopenia	0	16
Muscle weakness	63	45
Myalgia	75	58
Sclerodactyly	50	62
Diffuse scleroderma	50	28
Digital ulcer	50	28
Dilatation of esophagus	13	14
Lung fibrosis/interstitial pneumonitis	63	33
Pulmonary hypertension	13	3
Sicca complex	88**	21
Hypergammaglobulinemia	88	90
Anti-dsDNA Ab	75	68
Anti-Sm Ab	25	24
Anti-SS-A/Ro Ab	50	21
Anti-SS-B/La Ab	13	0
Hypocomplementemia ($CH_{50} < 25$)	13	24
Rheumatoid factor	88	67

Abs, antibodies; CNS, central nervous system; CK, creatine kinase; VC, vital capacity; dsDNA, double-stranded DNA; Ab, antibody

* $P < 0.001$; ** $P < 0.05$

Table 3. Clinical characteristics of MCTD patients who fulfilled criteria for RA

Clinical features	Patients (%)	
	Did fulfill criteria ($n = 8$)	Did not fulfill criteria ($n = 78$)
Raynaud's phenomenon	100	100
Swollen fingers/hand	100	100
Joint involvement		
Morning stiffness	100*	3
Arthralgia	100	94
Arthritis	100	90
Persistent arthritis (>6 weeks)	100	4
Symmetrical arthritis	75*	5
Deformity	75*	0
Erosion (bone radiography)	100*	1
Photosensitivity	0	11
Malar rush	13	13
Alopecia	13	6
Pleuritis	0	8
Pericarditis	13	5
Lymphadenopathy	50	33
CNS involvement	13	3
Proteinuria	38	51
Hemolytic anemia	13	3
Leukopenia	75	65
Thrombocytopenia	13	14
Muscle weakness	75	44
Myalgia	75	58
Sclerodactyly	25	65
Diffuse scleroderma	75**	24
Digital ulcer	50	28
Dilatation of esophagus	38	11
Lung fibrosis/Interstitial pneumonitis	63	33
Pulmonary hypertension	0	4
Sicca complex	50	24
Hypergammaglobulinemia	88	90
Anti-dsDNA Ab	63	69
Anti-Sm Ab	13	26
Anti-SS-A/Ro Ab	25	23
Anti-SS-B/La Ab	0	1
Anti-CCP Abs	50**	5
Hypocomplementemia ($CH_{50} < 25$)	13	24
Rheumatoid factor	100	68

* $P < 0.001$; ** $P < 0.05$

(63%), symmetrical arthritis (63%), joint deformity (50%), and radiographic erosions (63%), were all significantly more common in anti-CCP-positive patients than in anti-CCP-negative patients ($P < 0.001$). In addition, there was a tendency for clinical features associated with SSc to be more common in anti-CCP-positive patients, and the sicca complex showed a significantly higher prevalence in those patients than in patients without anti-CCP antibodies ($P < 0.05$).

When the clinical features of MCTD patients who fulfilled the criteria for RA were compared with those of the patients who did not (Table 3), the MCTD patients with RA had a significantly higher frequency of diffuse scleroderma than the patients without RA ($P < 0.001$) in addition to their significantly higher frequency of anti-CCP antibodies ($P < 0.05$).

Disease spectrum of MCTD patients who fulfilled the criteria for RA and MCTD patients with anti-CCP antibodies who did not fulfill criteria for RA

Because the MCTD patients who fulfilled the diagnostic criteria for RA and the MCTD patients with anti-CCP antibodies had a higher prevalence of diffuse scleroderma and sicca syndrome, respectively, the overlapping clinical features of these patients were further analyzed (Table 4). All eight MCTD patients who fulfilled the criteria for RA were diagnosed as having at least two connective tissue diseases in addition to RA; and all the patients with anti-CCP antibodies had a disease spectrum that encompassed SLE and SSc.

In contrast, all of the anti-CCP-positive patients who did not fulfill the criteria for RA were diagnosed as having SjS

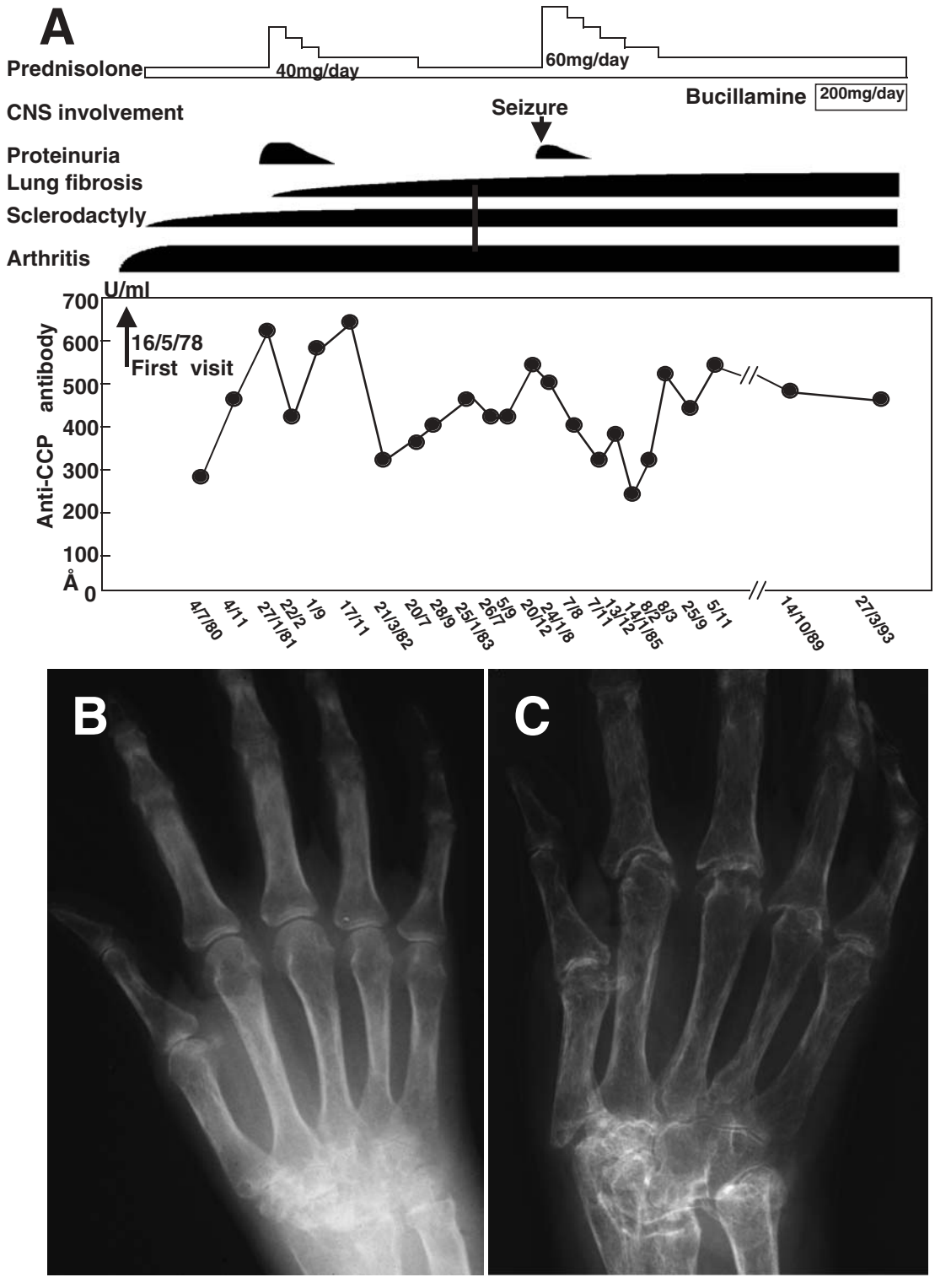

Fig. 2. Clinical course of patient 6 and anti-CCP antibodies. MCTD patient 6 first visited Juntendo hospital on May 16, 1978 (**A**). The initial diagnosis was SLE. The patient had arthritis of both wrists, but there were no radiographic changes that suggested RA. Anti-CCP antibodies were initially detected on July 4, 1980, and the patient was diagnosed as having RA in early 1981. At that time, the patient had persistent arthritis of both wrists, and destructive changes of the joints could be observed on hand radiographs (**B**). Despite treatment with a high dose of prednisolone, anti-CCP antibodies remained high during the clinical course. In addition, destructive changes of the proximal interphalageal/metacarpophalangeal (PIP/MCP) joints, ulnar styloid process, and radioulnar joint, as well as carpal fusion, became progressively worse, as shown by a hand-wrist radiograph from September 20, 1985 (**C**)

Table 4. Disease spectrum of MCTD patients who fulfilled criteria for RA, and anti-CCP-positive MCTD patients who did not fulfill criteria for RA

Patient	Anti-CCP antibodies	Disease spectrum
MCTD patients who fulfilled the criteria (n = 8)		
Patient 1	−	RA + SLE + SSc
Patient 2	+	RA + SLE + SSc
Patient 3	+	RA + SLE + SSc + SjS
Patient 4	−	RA + SLE +SSc + PM
Patient 5	−	RA + SSc + SjS
Patient 6	+	RA + SLE + SSc + SjS
Patient 7	+	RA + SLE + SSc + SjS
Patient 8	−	RA + SLE + SSc + PM
MCTD patients who did not fulfill the criteria (n = 4)		
Patient 9		SSc + SjS
Patient 10		SLE + SjS
Patient 11	+	SjS
Patient 12	+	SjS

and did not have the additional overlapping features of more than two other diseases (e.g., SLE and SSc) that fit the respective diagnostic criteria. These results suggested that anti-CCP antibodies are related to the presence of RA in MCTD patients who have overlapping features of SLE and SSc or to the presence of SjS in MCTD patients who do not have RA and other overlapping diseases.

Changes in anti-CCP antibodies during the clinical course

To further study the clinical significance of anti-CCP antibodies in MCTD patients, the association between antibody titers and clinical features was longitudinally analyzed (Figs. 2, 3). MCTD patient 6 (in Table 4) first visited Juntendo Hospital on May 16, 1978. The initial diagnosis was SLE; the patient had arthritis of both wrists, but there were no radiographic changes that suggested RA. Anti-CCP antibodies were first detected on July 4, 1980, and the patient was diagnosed as having RA in early 1981 (Fig. 2A). At that time, there was persistent arthritis of both wrists, and joint destruction was observed on hand radiographs, as shown in Fig. 2B. Proteinuria then appeared, and nephritis developed during January 1981, after which the patient was treated with prednisolone (40 mg/day). The nephritis diminished, and a decrease of the anti-CCP antibody titer was seen after administration of prednisolone, although the titer was still higher than 250 U/ml. The disease flared up again, and a seizure occurred on January 16, 1984. The prednisolone dose was increased to 60 mg/day, and the anti-CCP antibody titer decreased to 220 U/ml. Despite treatment with high doses of prednisolone, anti-CCP antibody titers stayed high, and destructive changes of the proximal interphalangeal/metacarpophalangeal (PIP/MCP) joints, ulnar styloid process, and radioulnar joint, as well as carpal fusion, became progressively worse. This is shown on the hand-wrist radiograph from September 20, 1985 (Fig. 2C) in comparison with the previous radiograph (Fig. 2B).

In contrast, MCTD patient 4 (Table 4) who first visited our hospital on October 1, 1982, was negative for anti-CCP antibodies on January 9, 1983 and remained negative until July 18, 1993, although this patient was always positive for RF (Fig. 3A). The patient had persistent arthritis of both wrists at the first visit, but there were no RA-like changes on radiographs. The initial diagnosis was MCTD. However, the patient began to fulfill the criteria for RA in 1984, showing typical changes on hand-wrist radiographs (Fig. 3B). Despite treatment with various disease-modifying antirheumatic drugs (DMARDs), including methotrexate (MTX), destructive changes of the hand and wrist joints became progressively worse, as shown in the radiograph from July 1993 (Fig. 3C).

Discussion

Rheumatoid arthritis, a systemic autoimmune disease of unknown etiology, is characterized by chronic inflammation of the joints that leads to tissue degradation and joint deformity; it is also part of the disease spectrum of MCTD.[4–9] Since it was reported by Waaler in 1940 and Rose et al. in 1948, RF has been widely used to diagnose RA. However, there has been a need for a substitute marker that is more reproducible, easy to use, and efficient for the diagnosis of RA because the specificity of RF is limited.[10,11] Therefore, many investigators have attempted to find autoantibodies that are specific and sensitive for RA. Two highly RA-specific autoantibodies [antiperinuclear factor (APF)[22] and antikeratin antibody (AKA)[23]] detected by indirect immunofluorescence were discovered in 1964 and 1979, respectively. Subsequently, the target antigens of APF and AKA were revealed to be filaggrin and related proteins,[24–26] and they were both designated antifilaggrin antibodies (AFAs). Identification of filaggrin as the target antigen led to the development of AFA assays based on immunoblotting[27] and ELISA[28] results, but their sensitivities were lower than that of RF, although both assays were demonstrated to be as specific as APF or AKA.

To solve this problem, a new assay for AFA has been developed based on a synthetic cyclic citrullinated peptide (CCP) with a sequence derived from human filaggrin.

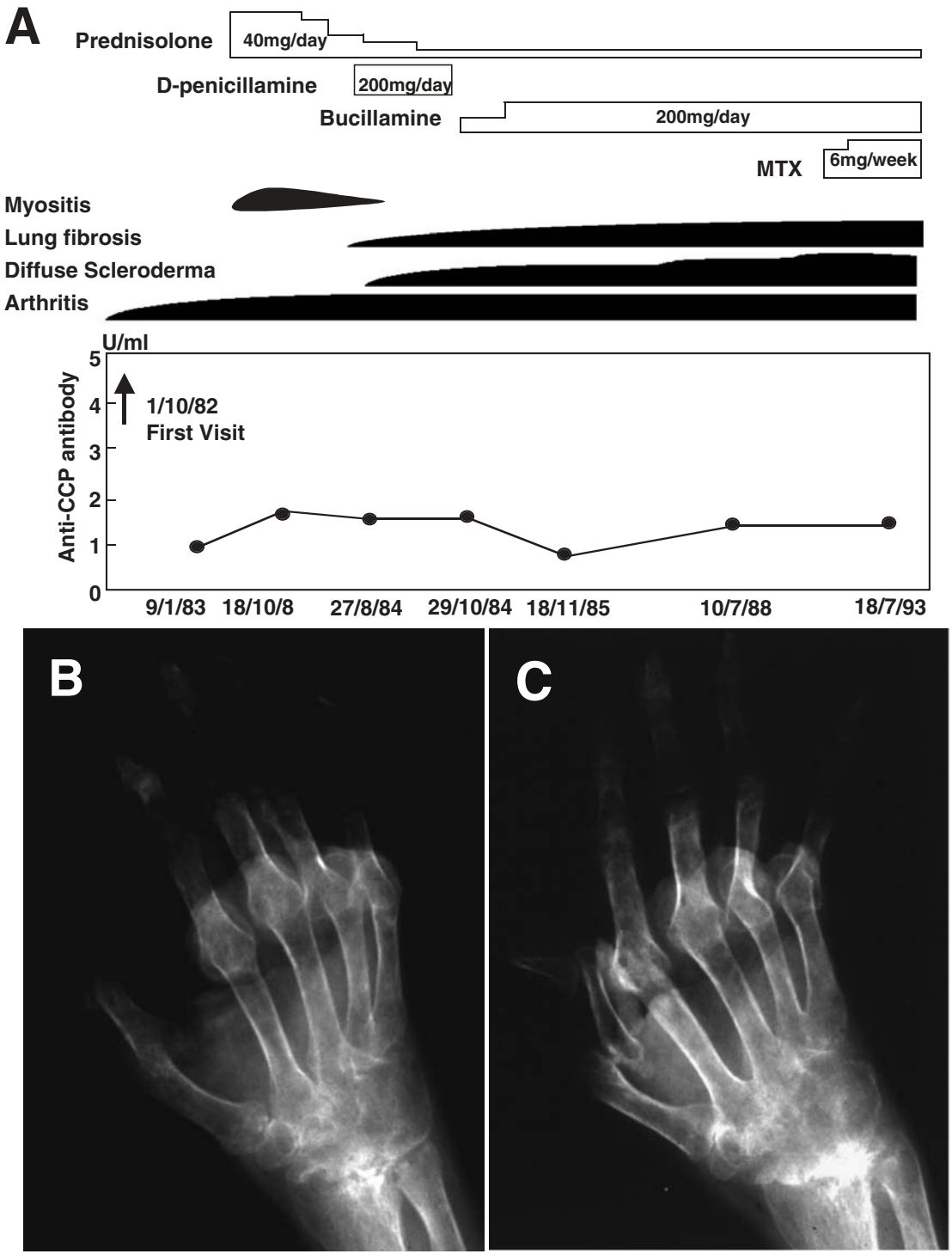

Fig. 3. Clinical course of patient 4 and anti-CCP antibodies. In contrast to patient 6, patient 4 first visited our hospital on October 1, 1982 and was negative for anti-CCP antibodies from January 9, 1983 to July 18, 1993, although this patient was always positive for rheumatoid factor (RF) (**A**). The patient also had persistent arthritis of both wrists at the first visit, but there were no RA-like changes on radiographs and the initial diagnosis was MCTD. However, the patient began to fulfill the criteria for RA in 1984, showing typical changes on hand-wrist radiographs (**B**). Despite treatment with various disease-modifying antirheumatic drugs (DMARDs), including methotrexate (MTX), destructive changes of the hand and wrist joints became progressively worse, as shown by the radiograph from July 1993 (**C**)

The basis of this development was that a recent study revealed that citrulline, which is created through posttranslational modification of arginine by peptidylarginine deiminase (PAD), is the essential constituent of the epitope recognized by APF and AKA.[10–14] Vossenaar et al. developed the original anti-CCP ELISA, and they recently reported that a search of their peptide libraries had led to the development of a second-generation anti-CCP assay,[29] which showed increased sensitivity for RA (from 60%–68% to 75%–80%) and retained a high specificity (98%).[10–14] We used this second-generation anti-CCP ELISA in the present study.

Although many investigators have shown that anti-CCP antibodies are useful for diagnosing RA (even early disease) and for evaluating the prognosis,[10–14] the specificity of these antibodies for destructive arthritis in other connective tissue diseases such as MCTD has not been well defined. In the present study, we found that anti-CCP antibodies were well correlated with RA-like clinical features (e.g., morning stiffness, persistent and symmetrical arthritis, joint deformity) and could be detected in 50% of MCTD patients who fulfilled the criteria for RA. In fact, anti-CCP antibodies were helpful for diagnosing patients who developed RA among 86 MCTD patients, of whom more than 90% had arthritis that was sometimes difficult for clinicians to distinguish from RA.[8] However, the frequency of antibody positivity (50%) was significantly lower than in RA patients, and four of eight MCTD patients fulfilling the criteria for RA were negative for anti-CCP antibodies, although all eight patients had severe destructive changes of their joints on radiographs.

A possible factor leading to the low prevalence of anti-CCP antibodies in MCTD patients was modification by treatment because these patients were often on steroids. To clarify this issue, we performed a longitudinal study and found that anti-CCP antibodies could persist despite administration of high-dose predonisolone, as shown during the clinical course of patient 6. Serum samples from three of the four MCTD patients who fulfilled the criteria for RA but were negative for anti-CCP were obtained before the administration of high-dose steroids. In fact, patient 4 was negative for anti-CCP antibodies throughout the clinical course, despite developing severe destructive arthritis (seen on hand-wrist radiographs). These results suggest that the type of treatment was not crucial for deciding anti-CCP positivity in MCTD patients.

The other possibility is a different pathogenesis of destructive joint changes among MCTD patients because RA is known to be a complex, diverse condition. It is well known that destructive arthritis can occur in patients with overlapping SLE and SSc, or with SSc,[4,8,30] and the characteristic arthritis is limited to the hands, wrists, or feet, as in patients with MCTD.[4–9] In fact, all eight MCTD patients (except patient 5) who fulfilled the criteria for RA also had a significantly higher frequency of diffuse scleroderma and the SLE and SSc overlap syndrome; these patients also showed severe destructive changes of their hands and wrists, whereas changes of other joints in the lower and upper extremities were limited. These features are different from those of typical RA,[4,8] and it is possible that different subsets of RA coexist among MCTD patients. Of course, even 20%–30% of patients with RA are negative for anti-CCP antibodies,[10–14] but the pathological and immunological differences between anti-CCP-positive and anti-CCP-negative RA patients have not been well defined. Further analysis of the immunological and pathological features of anti-CCP-positive patients may shed some light on the mechanisms leading to destructive changes associated with these antibodies.[10–14,29]

Our other interesting observation was that 50% of MCTD patients with anti-CCP antibodies did not fulfill the diagnostic criteria for RA. These patients obviously showed different clinical characteristics, as they had SjS and fulfilled the criteria for only MCTD or one additional disease. Hence, they were quite unlike the patients who fulfilled criteria for RA and had SEL and SSc overlap syndrome. An additional important observation was that the anti-CCP titers were lower in patients without destructive changes of their joints than in the four MCTD patients who fulfilled the criteria for RA, as shown in Fig. 1. Although previous studies have suggested that anti-CCP antibodies are highly specific for RA, except juvenile RA,[10–14,31,32] Mignot-Grootenberg et al. suggested an association of anti-CCP antibodies with primary SjS.[33] Because the prevalence of anti-CCP antibodies was also highest in SjS patients (18%) among the connective tissue diseases other than RA, and the frequency of sicca complex was significantly higher in MCTD patients with anti-CCP antibodies (Table 2) in the present study, it is possible that the anti-CCP antibodies in MCTD patients, including the four MCTD patients who fulfilled the criteria for RA, were associated with SjS.

Finally, the present study revealed that anti-CCP antibodies were useful for diagnosing RA in MCTD patients and could detect 50% of the patients who fulfilled diagnostic criteria for RA, although 50% of anti-CCP-positive patients did not fulfill these criteria. These results suggest that initiation of DMARD therapy must be considered when MCTD patients are positive for anti-CCP antibodies at a high titer and have SLE and SSc overlap syndrome with diffuse scleroderma because their arthritis is resistant to steroid therapy, as observed in our patients and noted in previous reports.[8] At the same time, we must be careful about administering DMARD therapy to anti-CCP-positive MCTD patients if they lack features of SLE and SSc.

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