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Radiological images of interstitial pneumonia in mixed connective tissue disease compared with scleroderma and polymyositis/dermatomyositis

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ABSTRACT

Objective: Little has been reported on the radiological and pathological findings of interstitial pneumonia in mixed connective tissue disease (MCTD). There may be possible difference in treatment response and prognosis between the imaging patterns of systemic sclerosis (SSc)-like and polymyositis/dermatomyositis (PM/DM)-like. The purpose of this study was to examine whether the radiological images of interstitial pneumonia in MCTD presented SSc-like or PM/DM-like pattern, and to assess whether the imaging patterns corresponded to clinical and pathological features.

Materials and methods: This retrospective study included 29 patients with interstitial pneumonia who underwent surgical lung biopsy; 10 with SSc, 10 with PM/DM, and 9 with MCTD. High resolution computed tomography (HRCT) images were classified as SSc, PM/DM, or the other pattern by two radiologists independently without clinical information. The pathology of the lung specimens from MCTD patients were evaluated and compared with the imaging pattern.

Results: The concordance rate between clinical diagnosis and radiological pattern was 100% in SSc patients, and 80% in PM/DM patients. Among patients with MCTD, imaging patterns were classified as SSc pattern in 4 (MCTD-SSc), PM/DM pattern in 4 (MCTD-PM/DM) and other in one. The imaging patterns did not always correlate with the clinical findings in MCTD patients. Pathologically, plasma cell infiltration and organizing pneumonia were relatively more frequent in MCTD-PM/DM, and smooth muscle hyperplasia was relatively more frequent in MCTD-SSc.

Conclusion: HRCT images in MCTD patients can be classified as SSc pattern or PM/DM pattern. MCTD-SSc and MCTD-PM/DM were corresponded to similar pathological findings of SSc and PM/DM.

1. Introduction

Mixed connective tissue disease (MCTD) is characterized by a combination of symptoms seen in several different connective tissue diseases (CTDs): systemic scleroderma (SSc), polymyositis/dermatomyositis (PM/DM) and systemic lupus erythematosus (SLE) [1–5], presenting with a high positive titer of serum anti-U1-ribonucleoprotein (RNP) antibodies.

Interstitial pneumonia is an important prognostic factor in various CTDs, including MCTD, SSc and PM/DM [6]. Patients with SSc and PM/DM reportedly have interstitial pneumonia with features characteristic for each of the underlying diseases in terms of images, pathology and clinical course. In patients with SSc, high resolution computed tomography (HRCT) commonly shows ground-glass opacities (GGOs) and fine reticular opacities, often located posteriorly and subpleurally with sparing of the extreme periphery [7–10]. The pathological findings commonly demonstrate non-specific interstitial pneumonia (NSIP), predominantly fibrotic, with usual interstitial pneumonia (UIP) being

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the second most common pattern [11–14]. In contrast, HRCT in patients with PM/DM shows consolidation and prominent loss of volume predominantly in the lower lungs, often with traction bronchiectasis, GGOs, reticulation, and thickening of the bronchovascular bundles [7,15–18]. The most common pathological pattern in these cases are fibrotic and cellular NSIP or organizing pneumonia, although those two entities frequently coexist [7,19].

Reports on interstitial pneumonia in MCTD are limited [20,21], despite prevalence of the lung disease as high as 20%–65% [5]. Previous studies indicated that reticular opacities and GGOs were present predominantly in the peripheral and lower lung fields on HRCT, with traction bronchiectasis seen in 20–45% and consolidation in 0–27% of cases [20,22–24]. Assuming that the imaging patterns of interstitial pneumonia in MCTD resemble those in SSc or PM/DM, it may be that treatment response and prognosis would also differ between patients with SSc-like imaging pattern of and PM/DM-like pattern. The purpose of this study was to investigate whether radiological images of interstitial pneumonia in MCTD match the patterns seen in SSc or PM/DM and also if the clinical and pathological features of the disease differ according to the imaging patterns.

2. Materials and methods

2.1. Patients

This retrospective study was approved by the institutional review board and waived the need for informed consent. The retrospective study included 29 patients with interstitial pneumonia who underwent surgical lung biopsy in our hospital between April 1999 and May 2013, consecutive 10 patients with SSc, 10 with PM/DM, and 9 with MCTD. Patients were excluded if they were taking steroids at the first visit, had amyopathic dermatomyositis, or were diagnosed Sjogren's syndrome. The CTDs in each of the 29 patients had been diagnosed by a rheumatologist according to each diagnostic criteria [25–28]. Clinical information collected from the patients' medical records included age at biopsy, gender, smoking history, and pulmonary or extrapulmonary manifestations of their disease.

HRCT scan just before the lung biopsy was obtained during inspiration with the patient lying supine. For one patient, conventional CT data was obtained with 2-mm collimation and an 8-mm interval (X-Vigor or Aquillion-64, Toshiba, Tokyo, Japan), while for the other 28, a multi-detector row CT scanner was used to provide 0.5–1-mm slice thickness contiguous scans (Aquillion-16, Toshiba, Tokyo, Japan). Two radiologists examined the CT images with a commercially available DICOM viewer (EV Insite™, PSP Corporation, Tokyo, Japan) on high resolution liquid crystal display monitors. Laboratory findings and respiratory function tests, including forced vital capacity, forced expiatory volume in 1 s and carbon monoxide diffusing capacity, had been performed around the same time as the HRCT was done.

2.2. Methods of data analysis

The HRCT images were evaluated for consolidation, defined as areas of homogeneous increased attenuation that obscured the pulmonary vasculature; GGOs, defined as areas of hazy increased attenuation with preservation of bronchial and vascular margins; reticular opacities, defined as thickening of the intralobular interstitium; interlobular septal thickening; traction bronchiectasis, defined as irregular bronchial dilatation within or around areas with parenchymal abnormality; honeycombing, defined as areas of cystic spaces with thickened walls; micronodules, defined as discrete, small, round, focal opacities less than 3 mm in diameter; emphysema, defined as focal areas of low attenuation without visible walls; air trapping, defined as a mosaic appearance exaggerated on expiratory images; pleural effusion; pleural thickening; esophageal dilatation, defined as a luminal coronal diameter of ≥10 mm below the level of the aortic arch; lymphadenopathy, defined

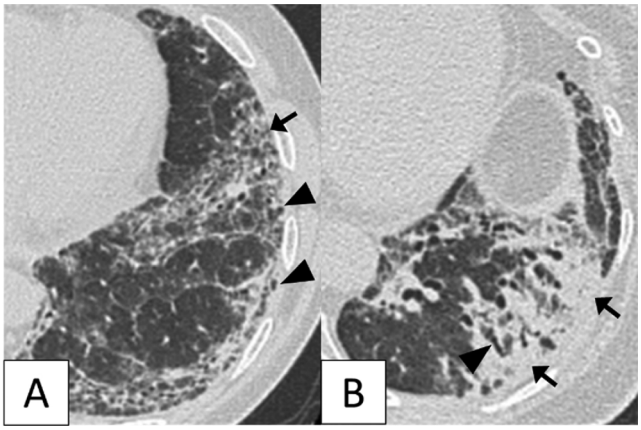

Fig. 1. Typical CT images of interstitial lung disease-associated connective tissue disease. **A**, CT image at the level of the lung base in a 62-year-old woman with systemic scleroderma shows reticular opacity (arrow) and traction bronchiectasis (arrowheads). **B**, CT image at the level of the lung base in a 64-year-old woman with dermatomyositis shows consolidation (arrows) and traction bronchiectasis (arrowheads).

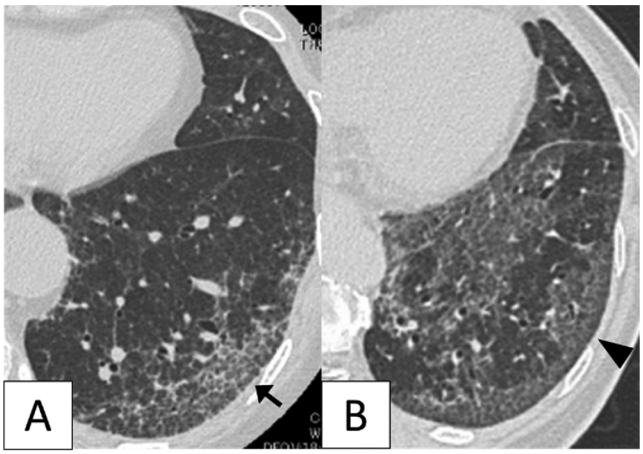

Fig. 2. CT images at the level of the lung base in patients with mixed connective tissue disease-systemic scleroderma pattern. **A**, CT image in a 58-year-old woman shows reticular opacity (arrow). **B**, CT image in a 54-year-old woman shows ground-glass opacity (arrowheads).

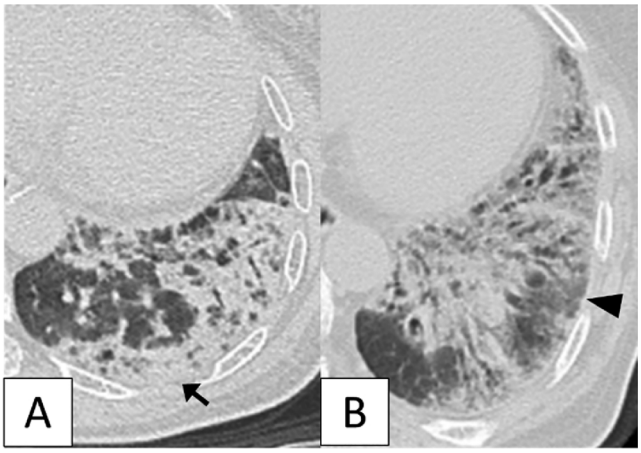

Fig. 3. CT images at the level of the lung base in patients with mixed connective tissue disease-polymyositis/dermatomyositis pattern. **A**, CT image in a 68-year-old woman shows consolidation (arrow). **B**, CT image in a 54-year-old woman shows consolidation (arrow) and ground-glass opacity (arrowhead).

Table 1
Patients characteristics.

	SSc	PM/DM		MCTD			
			p value[a]	MCTD-SSc	MCTD-PM/DM	p value[b]	MCTD-other
Patients	10	10		4	4		1
Age mean (range), years	61.0 (54–74)	64.8 (48–74)	0.239	62.3 (54–75)	54.0 (32–70)	0.335	17
Female	8	7	0.652	3	3	> 0.999	0
Former/current smoker	4	5	0.653	1	0	0.423	0
Clinical findings							
Raynaud's phenomenon	8	0	< 0.001	3	4	0.423	0
Polyarthritis	0	4	0.025	3	2	0.519	1
Swollen hands	2	1	0.531	2	2	> 0.999	0
Sclerodactyly	6	0	0.003	1	2	0.423	0
Myositis	0	10	< 0.001	2	1	0.423	0
Esophageal hypomotility	1	0	0.305	1	1	> 0.999	0
Aseptic meningitis	0	0	> 0.999	0	1	0.423	0
Pleuritis	0	1	0.305	1	0	0.423	0
Pericarditis	0	0	> 0.999	0	0	> 0.999	1
Pulmonary hypertension	2	0	0.136	1	0	0.423	0
Laboratory findings							
LDH (U/l)	244 ± 31	313 ± 78	0.052	308 ± 104	239 ± 56	0.429	185
CK (U/l)	80 ± 28	412 ± 624	0.023	160 ± 97	139 ± 98	0.546	33
CRP (mg/dl)	0.66 ± 1.00	1.07 ± 1.14	0.043	0.49 ± 0.51	0.20 ± 0.34	0.958	0.1
KL-6 (IU/ml)	1233 ± 871	1424 ± 696	0.353	2016 ± 1110	2134 ± 1330	0.875	1920
Respiratory function							
%FVC	94.3 ± 11.2	73.9 ± 13.8	0.002	82.1 ± 7.4	66.6 ± 18.7	0.172	43.8
FEV1/FVC (%)	80.4 ± 5.3	81.2 ± 6.0	0.880	83.5 ± 3.3	83.0 ± 7.7	0.695	81.4
%DLco	73.9 ± 16.2	69.0 ± 14.9	0.645	72.0 ± 15.3	64.2 ± 28.3	0.216	43.3
Interval between onset and HRCT, month	72 (1-240)	9.4 (1-60)	0.018	22 (6-55)	3.5 (1-5)	0.158	23

SSc, systemic sclerosis; PM-DM, polymyositis and dermatomyositis; MCTD, mixed connective tissue disease; LDH, lactate dehydrogenase; CK, creatine kinase; CRP, C-reactive protein; KL-6, Krebs von den Lugen-6; FVC, forced vital capacity; FEV1, forced expiatory volume in 1 s; DLCO, diffusing capacity of lung for carbon monoxide; HRCT, high resolution computed tomography.

[a] SSc vs. PM/DM.

[b] MCTD-SSc vs. MCTD-PM/DM.

Table 2
Inter-class Reliability.

Findings	kappa Coefficient
Parenchyma	
Consolidation	0.54
Ground-glass opacity	NA
Reticular opacity	0.45
Interlobular septal thickening	0.59
Traction bronchiectasis	0.44
Honeycombing	1.00
Micronodules	0.08
Emphysema	0.52
Air trapping	0.11
Mediastinum	
Pleural effusion	1.00
Pleural thickening	NA
Esophageal dilatation	0.61
Lymphadenopathy	0.02
Pulmonary artery dilatation	NA
Distribution	
Peribronchovascular	0.34
Subpleural	0.31
Radiological pattern	0.65

NA = not available.

as lymph nodes with a ≥1 cm short-axis diameter; and pulmonary artery dilatation, defined as the ratio of the main pulmonary artery to the ascending aorta ≥1. The spatial distributions of abnormalities were designated as peribronchovascular, defined as the region around a bronchus and artery; subpleural, defined as the region within 2 cm of the pleural surface; or diffuse, defined as both peribronchovascular and subpleural. The predominant findings and HRCT patterns were classified into three patterns: SSc pattern, characterized by GGOs and fine reticular opacities in a peribronchovascular distribution with subpleural sparing and lower lobe predominance [7–10] (Fig. 1A); PM/DM pattern, characterized by consolidation with associated collapse predominantly in the lower lung and traction bronchiectasis [7,15–18] (Fig. 1B); or the other pattern [29,30].

For this study, two chest radiologists who were unaware of the clinical information and diagnoses retrospectively and independently evaluated the lung HRCT findings. Disagreements between them after their first assessment were resolved by discussion. The kappa coefficient was used to measure their inter-rater reliability, with coefficients of < 0.21, 0.21–0.40, 0.41–0.60, 0.61–0.80, and > 0.80 considered to indicate poor, fair, moderate, good, and excellent agreement, respectively.

Lung biopsy specimens of MCTD patients were evaluated by a pathologist with expertise in interstitial pneumonia who was unaware of the HRCT pattern. Pathological features were semi-quantitatively graded as 0 (absent), 1 (mild: < 25%), 2 (moderate: 25–50%), or 3 (severe: > 50%). The following features were assessed: interstitial inflammation, plasma cell infiltration, interstitial fibrosis, smooth muscle hyperplasia, lymphoid follicles with germinal centers, organizing pneumonia, fibroblastic foci, microscopic honeycombing, emphysema, cysts, cellular bronchiolitis, bronchiolar fibrosis, thickening of the vascular intima and media, perivascular collagen deposition, and pleuritis. The pathological assessments were made with reference to previous studies [31–33], and correlations between HRCT findings and pathological findings were analyzed.

2.3. Statistical analysis

Fisher's exact test was used to compare categorical data, and the Mann-Whitney *U* test was used to compare continuous data and semi-quantitative grade. A *p* value of < 0.05 was considered statistically significant. Statistical analyses were performed using SPSS software version 24.0 (SPSS, Inc., Chicago, IL, USA).

Table 3
HRCT Findings.

	SSc	PM/DM		MCTD			
				MCTD-SSc	MCTD-PM/DM		MCTD-other
Findings	(n = 10)	(n = 10)	p value	(n = 4)	(n = 4)	p value	(n = 1)
Parenchyma							
Consolidation	4	10	0.011	2	4	0.429	0
Ground glass opacity	9	9	> 0.999	4	4	> 0.999	1
Reticular opacity	9	2	0.003	4	0	0.029	1
Traction bronchiectasis	10	7	0.105	4	4	> 0.999	0
Interlobular septal thickening	1	4	0.303	1	0	> 0.999	1
Honeycombing	1	0	> 0.999	0	0	> 0.999	0
Micronodules	0	0	> 0.999	2	0	0.429	1
Emphysema	1	2	> 0.999	0	0	> 0.999	1
Air trapping	1	0	> 0.999	0	1	> 0.999	0
Mediastinum							
Pleural effusion	0	1	> 0.999	0	0	> 0.999	0
Pleural thickening	0	0	> 0.999	0	0	> 0.999	0
Esophageal dilatation	1	0	> 0.999	1	1	> 0.999	0
Lymphadenopathy	7	8	> 0.999	3	4	> 0.999	0
Plumonary artery dilatation	0	0	> 0.999	0	0	> 0.999	0
Distribution							
Peribronchovascular	7	10	0.105	1	4	0.143	1
Subpleural	7	6	> 0.999	4	2	0.429	1
Diffuse	1	0	> 0.999	0	0	> 0.999	0

SSc, systemic sclerosis; PM-DM, polymyositis and dermatomyositis; MCTD-SSc, mixed connective tisue disease which classified SSc pattern; MCTD-PM/DM, mixed connective tisue disease which classified PM/DM pattern.

Table 4
Predominant HRCT Findings.

	SSc	PM/DM		MCTD			
				MCTD-SSc	MCTD-PM/DM		MCTD-other
	(n = 10)	(n = 10)	*p* value	(n = 4)	(n = 4)	*p* value	(n = 1)
Predominant findings			0.001 >			0.018	
Consolidation	0	9		0	4		0
Ground-glass opacity	4	1		1	0		1
Reticulation	6	0		3	0		0
Predominant distribution			0.273			0.486	
Peribronchovascular	6	9		1	3		1
Subpleural	3	1		3	1		0
Diffuse	1	0		0	0		0

SSc, systemic sclerosis; PM-DM, polymyositis and dermatomyositis; MCTD-SSc, mixed connective tissue disease classified as a SSc pattern; MCTD-PM/DM, mixed connective tissue disease classified as a PM/DM pattern.

3. Results

3.1. Patient characteristics

Among the 9 patients with MCTD, HRCT patterns were classified as SSc pattern in 4 patterns (MCTD-SSc, Fig. 2), PM/DM pattern in 4 (MCTD-PM/DM, Fig. 3), and other in one (MCTD-other). The concordance rate between the clinical diagnosis and radiological pattern assessed by two blinded radiologists was 100% for the 10 patients with SSc, and 80% for the 10 with PM/DM.

The characteristics, clinical findings, laboratory results, and pulmonary function of the 29 study patients are summarized in Table 1. Age, sex, and smoking history did not differ significantly. Women predominated in all groups except for the patients with the MCTD-other pattern who was a young man. Raynaud's phenomenon and sclerodactyly were more common ($p < 0.001$, $p = 0.003$, respectively) in SSc than in PM/DM, but this tendency was not seen in MCTD-SSc. Similarly, polyarthritis and myositis were more common in PM/DM ($p = 0.025$, $p < 0.001$, respectively), but not in MCTD-PM/DM. Creatine kinase and C-reactive protein levels were higher in PM/DM was higher than that in SSc, but these laboratory values did not differ significantly between MCTD-SSc and MCTD-PM/DM.

In SSc, percentage forced vital capacity (%FVC) was higher than that in PM/DM, although the average interval between disease onset and pulmonary function tests was longer in SSc (72.4 vs. 9.4months, p = 0.018). The corresponding average interval and before testing and %FVC were relatively, but not significantly, longer and higher in MCTD-SSc than MCTD-PM/DM.

3.2. Inter-rater reliability

The kappa coefficients are summarized in Table 2. Although the first assessments for GGO, pleural thickening, and pulmonary artery dilatation were in agreement in 58.6% (17/29), 86.2% (25/29), and 75.9% (22/29) of cases, respectively, kappa coefficients could not be calculated because of the strong deviation of assessments, not because the degree of agreement was poor. Agreement between the radiologists was good in terms of defining the HRCT patterns.

Table 5
Pathological findings in the patients of MCTD.

	MCTD-SSc				MCTD-PM/DM					MCTD-other
Case No.	1 grade	2	3	4	1	2	3	4	p	1
Interstitial inflammation	2	2	3	1	3	3	2	2	0.343	1
Plasma cell infiltration	2	2	2	1	3	3	3	3	0.011	1
Interstitial fibrosis	2	3	3	2	3	3	1	2	0.752	1
Smooth muscle hyperplasia	1	1	1	1	0	0	0	0	0.008	1
Lymphoid follicles with germinal center	1	1	0	0	1	1	1	0	0.495	2
Organizing pneumonia	0	1	0	0	1	0	3	1	0.155	0
Fibroblastic foci	0	1	2	1	1	0	0	3	0.762	1
Microscopic honeycombing	0	0	1	0	1	0	0	0	1.00	0
Emphysema	0	0	1	0	0	0	0	1	1.00	2
Cysts	0	0	0	0	0	0	0	0	1.00	0
Cellular bronchiolitis	2	2	2	1	3	1	3	1	0.760	3
Bronchiolar fibrosis	0	0	0	0	1	0	0	0	0.317	1
Vascular intimal and medial thickening	1	2	0	1	0	3	1	0	0.762	0
Perivascular collagen deposition	3	0	1	1	0	1	1	0	0.343	1
Pleuritis	1	1	1	1	0	2	3	2	0.215	1
Pathological diagnosis	fNSIP	UIP	unclassifiable	unclassifiable	f NSIP	f NSIP	unclassifiable	fNSIP		unclassifiable

MCTD-SSc, mixed connective tisue disease which classified SSc pattern; MCTD-PM/DM, mixed connective tisue disease which classified PM/DM pattern; MCTD-other, mixed connective tisue disease which classified other pattern; UIP, usual interstitial pneumonia; fNSIP, fibrotic nonspecific interstitial pneumonia; cNSIP, cellular nonspecific interstitial pneumonia.

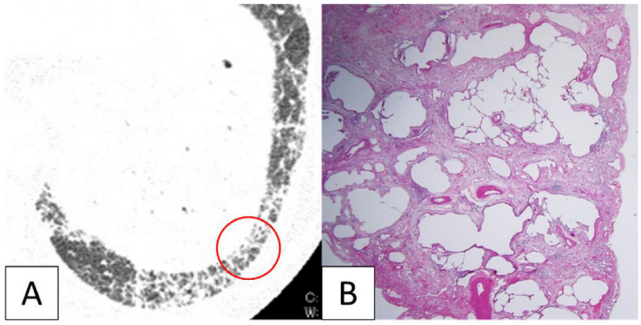

Fig. 4. Radiological and pathological findings in a 75-year-old woman with mixed connective tissue disease-systemic scleroderma. **A**, Reticular opacity can be seen in segment 9 (circle) on CT. **B**, Grade 3 interstitial fibrosis and grade 1 microscopic honeycombing compatible with usual interstitial pneumonia can be seen in the histological image.

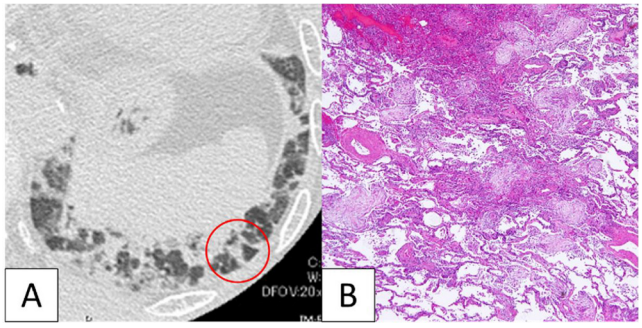

Fig. 5. Radiological and pathological findings in a 68-year-old woman with mixed connective tissue disease-polymyositis/dermatomyositis. **A**, Consolidation can be seen in segment 9 (circle) on CT. **B**, Grade 3 plasma cell infiltration, grade 3 organizing pneumonia, and grade 2 interstitial infiltration can be seen in the histological image.

3.3. Comparison of radiological findings

HRCT findings of these patients are summarized in Table 3. Consolidation was significantly more frequent in PM/DM (100%) than in SSc (40%) ($p = 0.011$). The frequency of reticular opacities was significantly higher in SSc (90%) than in PM/DM (20%) ($p = 0.003$). No significant differences were identified between SSc and PM/DM in the frequencies of other findings. In MCTD, GGOs and traction bronchiectasis were present in all patient. None of the patients with MCTD had honeycombing, pleural effusion, pleural thickening or pulmonary artery dilatation.

3.4. Comparison of predominant findings

The HRCT findings and their distribution in the three diseases are summarized in Table 4. Significant differences were identified between SSc and PM/DM ($p < 0.001$). In the 10 patients with SSc, the predominant findings were reticular opacities in 6 and GGOs in 4, whereas in the 10 with PM/DM consolidation was seen in 9 and reticular opacities in one. Significant differences were similarly identified between MCTD-SSc and MCTD-PM/DM ($p = 0.018$), with reticular opacities in one and GGOs in 3 of 4 patients with MCTD-SSc, and consolidation in all 4 with MCTD-PM/DM. However, there were no differences in the spatial distribution of abnormal shadows between SSc and PM/DM or between MCTD-SSc and MCTD-PM/DM. The one patient with MCTD-other had GGOs predominantly in peribronchovascular areas and extensive emphysema. These findings were a separate pattern altogether, not a mixture of SSc-like and PM/DM-like pattern.

3.5. Pathological investigation of MCTD

Pathological features in the 9 patients with MCTD are summarized in Table 5. The most common pathological features found in all patients were interstitial inflammation, plasma cell infiltration, interstitial fibrosis, and cellular bronchiolitis. The severity of plasma cell infiltration was significantly higher in MCTD-PM/DM ($p = 0.011$), and that of organizing pneumonia was also relatively higher in MCTD-PM/DM ($p = 0.16$). The severity of smooth muscle hyperplasia was significantly higher in MCTD-SSc ($p = 0.008$). Fibrosing NSIP and unclassifiable pattern were pathologically diagnosed in patients with both imaging patterns, and UIP was seen in one patient with MCTD-SSc.

A correlation between HRCT findings and pathological features was evaluated, focusing on the image of the region that had been biopsied. Patients with grade 3 plasma cell infiltration or grade 3 organizing

pneumonia had consolidation on HRCT. In those without pathologically defined organizing pneumonia, there was little, if any, consolidation. Reticular opacities correlated well with the degree of smooth muscle hyperplasia. In MCTD-SSc, interstitial fibrosis and microscopic honeycombing pathologically corresponded to reticular opacities on HRCT (Fig. 4). In MCTD-PM/DM, organizing pneumonia and interstitial inflammation corresponded to consolidation on HRCT (Fig. 5).

4. Discussion

In the present study, the majority of interstitial pneumonia in MCTD was radiologically classifiable into SSc pattern or PM/DM pattern according to HRCT images. The findings in patients in the MCTD-SSc and MCTD-PM/DM groups were similar to those in SSc and PM/DM, both radiologically and pathologically. Reticular opacities and consolidation were useful for distinguishing SSc from PM/DM radiologically in this study. One patient classified with MCTD-other pattern presented novel imaging pattern that did not present as a mixture of SSc and PM/DM patterns.

The rationale for distinguishing the radiological pattern of interstitial pneumonia in MCTD patients is that it may help in choosing among treatment options. In SSc, GGOs in fibrotic NSIP correspond not with inflammation but rather than with fibrosis which is irreversible despite treatment [7,34]. Corticosteroids have no apparent beneficial effect on pulmonary fibrosis; only oral cyclophosphamide has proven effective for treating interstitial pneumonia in SSc [35]. In patients with PM/DM, NSIP and organizing pneumonia are the most common pathological patterns and frequently coexist. [7,19], and they usually respond to corticosteroid treatment [36–38].

A previous study compared HRCT findings in MCTD, SSc, PM/DM, and SLE, but MCTD cases were summarized in one group for comparison with the other diseases. The conclusion of this study was that the CT findings in MCTD were a combination of those in the other CTDs [21]. However, our study is the first to indicate that HRCT imaging findings of interstitial pneumonia in MCTD patients may in fact be classifiable as either SSc or PM/DM pattern.

Despite the distinction between MCTD-SSc and MCTD-PM/DM on HRCT, clinical findings such as sclerodactyly (characteristic of SSc), and myositis or the increased creatine kinase levels (characteristic of PM/DM) and pulmonary function such as %FVC did not differ significantly among the patients with MCTD, although this result may be due to the small sample size.

Pathologically, MCTD-SSc significantly differed from MCTD-PM/DM in the severity of plasma cell infiltration and smooth muscle hyperplasia, and differed relatively, although not significantly, in the severity of organizing pneumonia. Plasma cell infiltration and organizing pneumonia are frequent in patients with PM/DM, and smooth muscle hyperplasia, a stage in the process of fibrosis, is found in patients with SSc [12,19]. Therefore, as suggested above, MCTD-PM/DM may respond well to treatment with steroid and immunosuppressive agents, while cyclophosphamide might be considered for patients with MCTD-SSc. It is thus possible that the clinical behavior of interstitial pneumonia in MCTD in terms of treatment response can be predicted on the basis of its HRCT image pattern.

There are several limitations to this study. First, as a retrospective, single-institution study with a small sample size, it is susceptible to all of the limitations and biases inherent in a retrospective design. Our results therefore may not be generalizable to all patients with MCTD. However, it would be difficult to perform a large-scale prospective study of such a rare disease. Second, we did not assesse patients with SLE in this study because interstitial lung disease is uncommon in SLE. Third, as many of the patients were eventually lost to follow-up, we could not assess disease behavior over time. In particular, we could not evaluate possible differences in treatment response between patients with MCTD-SSc and MCTD-PM/DM pattern. More patients who can be followed long-term are needed for such an assessment in the future.

In conclusion, HRCT images of interstitial pneumonia in MCTD can, with perhaps a few exceptions, be classified as matching SSc or DM/PM pattern. Pathological features in MCTD-SSc and MCTD-PM/DM also differ significantly, again resembling what is seen pathologically in SSc or PM/DM.

Conflict of interest

All authors have no conflict of interest directly relevant to the content of this article.

Authors' contributions

T.O., Y.Y., T.B. and F.S. were involved in conceptualization; Y.Y. and T.B. were involved in study design; Y.Y. and S.N. were involved in data acquisition; Y.Y., N.Y., T.T. and F.S. were involved in quality control of data and algorithms; Y.Y. and T.B. were involved in data analysis and interpretation; Y.Y. was involved in statistical analysis and manuscript preparation; Y.Y., T.B., E.H., N.Y. and F.S. were involved in manuscript editing; T.O., T.B., E.H., N.Y., T.T., S.N., F.S. and K.K. were involved in manuscript review.

IRB statement

This study was approved by the institutional review board of Kanagawa Cardiovascular and Respiratory Center.

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