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Connective Tissue Disease and its Evolution on Chest CT

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Abstract

Background/Objective: Evaluate the radiographic appearances most commonly associated with Connective Tissue Diseases (CTD) and their evolution over time.

Methods: This systematic review draws data from the IRB approved Mount Sinai Interstitial Lung Disease Registry with 381 enrolled patients at the time of this review. CT scans of 108 patients with a working diagnosis of connective tissue disease (CTD) were evaluated by a Radiologist (MS with 20 years of experience) a Pulmonologist (AM with 5 years of experience). The patient's first CT scan demonstrating fibrosis and every CT scan at least one year later were reviewed, and the pattern of fibrosis and extent of disease were recorded by consensus agreement.

Results: 108 patients out of 381(28%) had a working diagnosis of CTD based on clinical presentation, serologic markers and chest CT. 80 had multiple CT scans allowing follow-up over time. 35% of the patients had myositis. 24% of patients had a diagnosis of scleroderma (SC). The remaining had organizing pneumonia (OP) (11%), rheumatoid arthritis (RA) (8%), interstitial pneumonia with autoimmune features (IPAF) (6%), mixed connective tissue disease (MCTD) (5%), sjogren's (Sj) (5%), undifferentiated (UN) (4%) and vasculitis (V) (2%). The radiographic pattern of disease changed over time in 35%. 44% of patients with OP diagnosis returned to normal on follow-up. 50 (63%) of patients had worsening disease on CT over time. 12 (15%) decreased extent of disease or resolved. 18 (23%) remained stable.

Conclusion: There are many types of CTD with variable radiographic presentations, which can change over time. The diseases are frequently progressive with few returning to normal.

Keywords: Connective tissue disease; Pulmonary fibrosis, Organizing pneumonia; Nonspecific Interstitial pneumonitis; Usual interstitial pneumonitis

Key Points

a) Connective tissue disease can affect the lung and the presentation is variable.

b) Lung disease associated with connective tissue disease can progress over time.

c) The organizing pneumonia pattern can return to normal in many patients on follow-up imaging.

Introduction

There are many types of pulmonary fibrosis which are differentiated by their clinical presentation, radiology and pathology. The most common type of pulmonary fibrosis and the one with the highest morbidity and mortality is idiopathic pulmonary fibrosis (IPF). The pattern on CT scan is a usual interstitial pneumonitis (UIP) pattern which has been defined by the American Thoracic Society, the European Respiratory Society, the Japanese Respiratory Society, and the Latin American Thoracic Association (ATS/ERS/JRS/ALAT) as sub-pleural basilar predominant fibrosis with honeycombing [1]. New anti-fibrotic treatments slow the progression of the disease but do not reverse the disease so fibrosis on CT scans remains stable or progresses [2]. The CTDs affect younger individuals with a female predominance. The CTDs are subdivided based on clinical, radiology and serologic features. The findings on chest CT are more variable than with IPF. They can include nonspecific interstitial pneumonitis (NSIP), organizing pneumonia (OP), UIP, and even chronic hypersensitivity pneumonitis (CHP) patterns [3,4]. The pattern can change over time and even

resolve with treatment, making radiology diagnosis challenging. Understanding the most common patterns associated with each type of CTD and the evolution can help with diagnosis and treatment recommendations. The purpose of this paper is to evaluate the radiographic appearances most commonly associated with each CTD and their evolution over time.

Methods

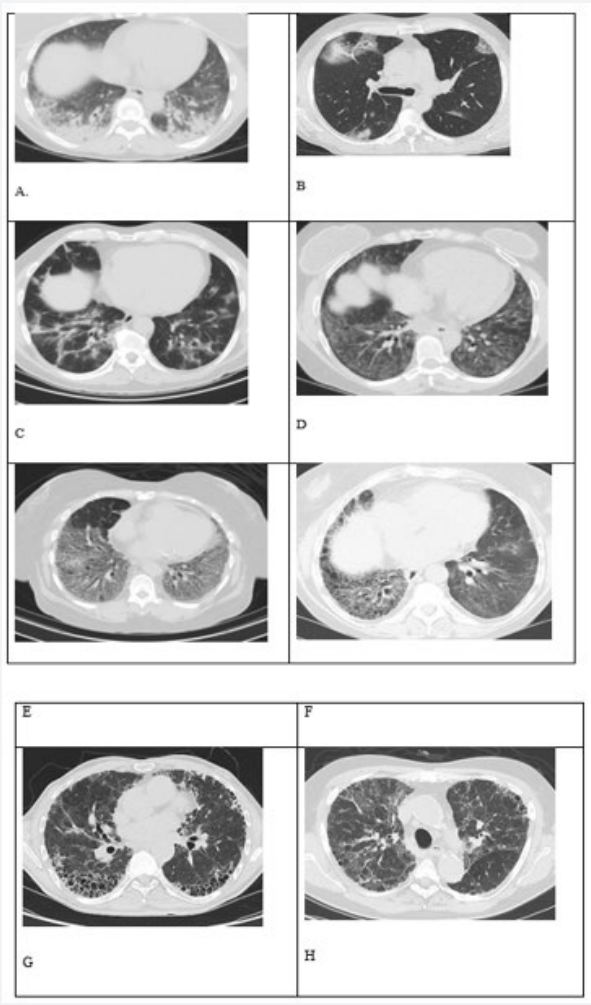

Figure 1: A) Peripheral organizing pneumonia (POP): Peripheral alveolar opacities. B) Bronchovascular organizing pneumonia (BOP): Alveolar opacities along the bronchovascular bundles. C) Nonspecific interstitial pneumonitis and organizing pneumonia (NSOP). D) Cellular nonspecific interstitial pneumonitis: homogeneous lower lobe predominant fibrosis with ground glass opacities. E) Mixed cellular and fibrotic nonspecific interstitial pneumonitis: homogeneous lower lobe predominant fibrosis with ground glass opacities and increasing bronchiectasis. F) Fibrotic nonspecific interstitial pneumonitis: homogeneous lower lobe predominant fibrosis with less ground glass opacities and more bronchiectasis. G) Usual interstitial pneumonitis: Subpleural basilar predominant fibrosis with honeycombing. H) Chronic hypersensitivity pneumonitis: Airway centered fibrosis with air trapping.

Internal Review Board approval was obtained. Our paper draws patients from the Mount Sinai ILD Registry, which at the time of the study contained 381 patients with pulmonary fibrosis among whom 108 had a CTD Working Diagnosis based on a multidisciplinary approach. Patients signed an informed consent to participate in the registry. The age and gender of each patient was recorded as well as the specific CTD diagnosis. The first CT scan with evidence of interstitial lung disease and all follow up CT scans that were at least 1 year apart were reviewed by a thoracic radiologist and pulmonologist and their consensus opinion was recorded. The date of the CT scan, the pattern of disease and the extent of disease were recorded. The grading of extent of disease was based on a previously reported grading system for lung fibrosis [5] (Table 1). The right upper lobe and right middle lobe are considered as one lobe in this grading system. The maximum score is 16. The pattern of disease is described in (Table2) (Figure1).

Table 1: Grading system for pulmonary fibrosis.

Right Upper Lobe	Left Upper Lobe
Grade 1: 1 to 10% fibrosis of lobe	Grade 1: 1 to 10% fibrosis of lobe
Grade 2: 11-25% fibrosis of lobe	Grade 2: 11-25% fibrosis of lobe
Grade 3: 26-50% fibrosis of lobe	Grade 3: 26-50% fibrosis of lobe
Grade 4: > 50% fibrosis of a lobe	Grade 4: > 50% fibrosis of a lobe
Right Lower Lobe	**Left Lower Lobe**
Grade 1: 1 to 10% fibrosis of lobe	Grade 1: 1 to 10% fibrosis of lobe
Grade 2: 11-25% fibrosis of lobe	Grade 2: 11-25% fibrosis of lobe
Grade 3: 26-50% fibrosis of lobe	Grade 3: 26-50% fibrosis of lobe
Grade 4: > 50% fibrosis of a lobe	Grade 4: > 50% fibrosis of a lobe

Table 2: Patterns of interstitial lung disease on chest CT.

Peripheral organizing pneumonia (POP)	Traditional pattern of peripheral consolidation.
Broncho vascular organizing pneumonia (BOP)	Consolidation along the Broncho vascular bundles.
Mixed organizing pneumonia (MOP)	Organizing pneumonia in a peripheral and Broncho vascular distribution.
Nonspecific interstitial pneumonitis and organizing pneumonia (NSOP)	Overlapping features of NSIP with areas of consolidation.
Cellular nonspecific interstitial pneumonitis (CNSIP)	Homogeneous lower lobe airway centered disease with ground glass opacity and limited bronchiectasis.
Mixed nonspecific interstitial pneumonitis (MNSIP)	Homogeneous lower lobe airway centered disease with ground glass opacity and bronchiectasis.
Fibrotic nonspecific interstitial pneumonitis (FNSIP)	Homogeneous lower lobe airway centered disease with bronchiectasis and limited ground glass opacity.
Usual interstitial pneumonitis (UIP)	Subpleural, basilar predominant fibrosis with honeycombing.
Chronic hypersensitivity pneumonitis (CHP)	Heterogeneous airway centered fibrosis often with air-trapping.

Results

108 patients out of 381(28%) had a working diagnosis of CTD. Of those 108 patients, 80 had multiple CT scans allowing

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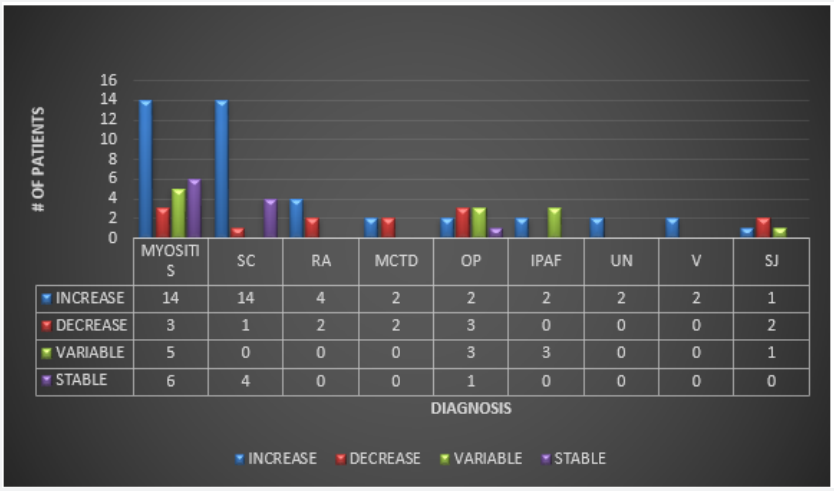
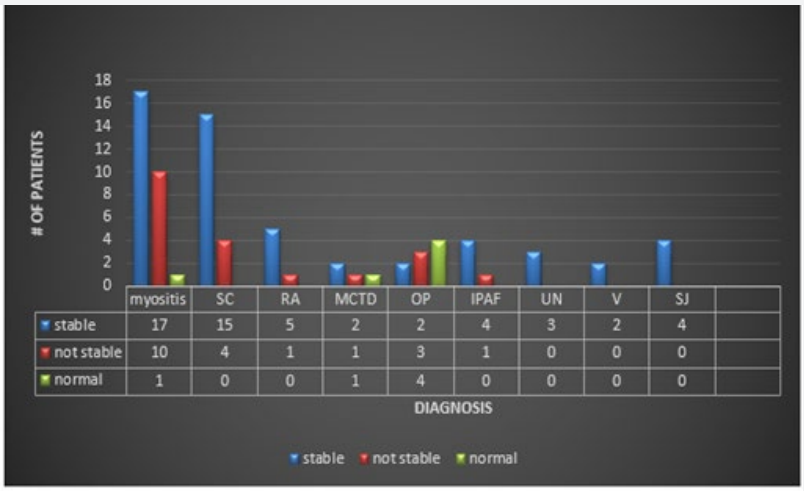
assessment of CT pattern and extent of disease over time. 28 (35%) of the patients had myositis which included dermatomyositis, polymyositis and antisynthetase diagnoses. 19 (24%) of patients with CTD had a diagnosis of scleroderma. The remaining patients had OP 9 (11%), RA 6 (8%), IPAF 5 (6%), MCTD 4 (5%), sjogren's 4 (5%), undifferentiated 3 (4%) and vasculitis 2 (2%). The oldest patients were in the idiopathic group and the youngest patients had a working diagnosis of MCTD. All patients with MCTD and sjogren's were females. Overall, 6 patients returned to normal on CT over the course of their disease, 4 of these patients had a diagnosis of organizing pneumonia. 50 (63%) of patients had worsening disease on CT over time. 12 (15%) decreased extent of disease or resolved. 18 (23%) remained stable. 36 patients had an NSIP pattern on first CT. 18 had OP, 14 had NSOP, 9 had UIP and 3 had CHP pattern (Figure 2 & 3).



	MYOSITIS	SC	RA	MCTD	OP	IPAF	UN	V	SJ
INCREASE	14	14	4	2	2	2	2	2	1
DECREASE	3	1	2	2	3	0	0	0	2
VARIABLE	5	0	0	0	3	3	0	0	1
STABLE	6	4	0	0	1	0	0	0	0

Figure 2: Change in extent of disease over time.



	myositis	SC	RA	MCTD	OP	IPAF	UN	V	SJ
stable	17	15	5	2	2	4	3	2	4
not stable	10	4	1	1	3	1	0	0	0
normal	1	0	0	1	4	0	0	0	0

Figure 3: Evolution of pattern of fibrosis for CTDs. Some have a stable pattern of fibrosis; others have a changing pattern of fibrosis and some return to normal.

Myositis-35% of the patients with CTD had myositis which included dermatomyositis, polymyositis and anti-synthetase diagnoses. The average age was 57 years old. The percentage of female patients was 46 %. NSIP and NSOP patterns were most common as seen with other researchers including Debray who found 45% had an NSIP pattern [6]. Half of the patient's extent of fibrosis progressed over the study interval however the pattern of disease remained relatively stable. 1/28 patients CT returned to normal (Table 3). Scleroderma-24% of patients with CTD had a diagnosis of scleroderma. The average age was 63 and 78% were women. The NSIP pattern was most common but a few people had a UIP pattern which is similar to other authors [7]. Many patients (74%) progressed and none returned to normal suggesting overall, that this is a CTD with a worse prognosis (Table 4). Organizing Pneumonia-11% of patients with CTD had OP. The average age in our study was 57 which was relatively young. Only 11% were female. As would be expected nearly all the patients had an OP pattern on CT as has been described in the literature. Nearly half improved over the course of follow-up but some had a waxing and waning course as is typical of the disease.

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Table 3: Pattern of fibrosis and extent of disease on first and last CT scan and time between imaging in patients with Myositis.

	Initial	Last	Total Time (months)
Polymyositis	NSOP 10	Normal	13
Polymyositis	MOP 16	CNSIP 8	35
Polymyositis	NSOP 4	MNSIP 7	110
Polymyositis	NSOP 4	MNSIP 7	83
Polymyositis	FNSIP 4	FNSIP 8	136
Antisynthetase	CNSIP 2	CNSIP 1	80
Antisynthetase	CNSIP2	MNSIP 11	44
Antisynthetase	CNSIP 6	MNSIP 8	17
Antisynthetase	CHP 7	CHP12	68
Antisynthetase	NSOP4	NSOP 14	35
Antisynthetase	NSOP 10	NSOP 12	16
Antisynthetase	OP 4	OP 7	28
Antisynthetase	NSOP 8	CNSIP 8	46
Antisynthetase	POP 8	CNSIP 10	54
Antisynthetase	NSOP 7	NSOP 6	81
Dermatomyositis	BOP 2	NSOP 4	32
Dermatomyositis	POP 1	MOP 6	35
Dermatomyositis	CNSIP 4	CNSIP 6	83
Dermatomyositis	CNSIP 2	CNSIP 4	115
Dermatomyositis	MNSIP 7	MNSIP 12	111
Dermatomyositis	NSOP 13	NSOP 14	21
Dermatomyositis	CNSIP 14	NSOP 14	20
Dermatomyositis	CHP 6	CHP 6	23
Dermatomyositis	MNSIP 6	MNSIP 6	123
Dermatomyositis	NSOP 16	NSOP 16	167
Dermatomyositis	BOP 4	BOP 4	41
Dermatomyositis	CNSIP 4	CNSIP 4	36
Dermatomyositis	NSOP 5	NSOP 5	60

Table 4: Pattern of fibrosis and extent of disease on first and last CT scan and time between imaging in patients with Scleroderma.

	Initial	Last	Total Time (Months)
Scleroderma	CNSIP 7	MNSIP 4	72
Scleroderma	CNSIP 2	CNSIP 4	33
Scleroderma	POP 8	POP 9	21
Scleroderma	CNSIP 4	MNSIP 4	104
Scleroderma	UIP 4	UIP 6	134
Scleroderma	UIP 12	UIP 16	29
Scleroderma	CNSIP 2	CNSIP 6	81
Scleroderma	MNSIP 10	MNSIP 10	53
Scleroderma	MNSIP 8	MNSIP 8	21
Scleroderma	MNSIP 8	MNSIP 8	11
Scleroderma	MNSIP 5	MNSIP 7	117
Scleroderma	CNSIP 4	CNSIP 8	123
Scleroderma	POP 2	CNSIP 3	19
Scleroderma	FNSIP 2	FNSIP 3	152
Scleroderma	CNSIP 1	CNSIP 3	63
Scleroderma	UIP 2	UIP 4	44
Scleroderma	POP 4	POP 6	18
Scleroderma	CNSIP 4	CNSIP 5	12
Scleroderma	UIP 10	UIP 16	28

Table 5: Pattern of fibrosis and extent of disease on first and last CT scan and time between imaging in patients with organizing pneumonia.

	Initial	Last	Total Time (months)
OP	CNSIP 7	CNSIP 7	117
OP	BOP 7	NORMAL	24
OP	MOP 8	NORMAL	15
OP	MOP 4	MOP 4	61
OP	MOP 10	NORMAL	38
OP	NSOP 9	CNSIP8	43
OP	NSOP 6	NORMAL	24
OP	POP 2	FNSIP 6	35
OP	POP 2	FNSIP 7	147

Table 6: Pattern of fibrosis and extent of disease on first and last CT scan and time between imaging in patients with rheumatoid arthritis.

	Initial	Last	Total Time (months)
RA	CNSIP 3	MNSIP 6	42
RA	CHP 10	CHP 14	76
RA	UIP 4	UIP 8	87
RA	UIP 6	UIP 10	36
RA	CNSIP 12	CNSIP 12	18
RA	UIP 5	UIP 5	13

Table 7: Pattern of fibrosis and extent of disease on first and last CT scan and time between imaging in patients with rheumatoid arthritis.

	Initial	Last	Total Time (months)
IPAF	CNSIP 6	FNSIP 12	86
IPAF	NSOP 12	NSOP 12	26
IPAF	NSOP 3	NSOP 3	100
IPAF	MNSIP 6	MNSIP 10	13
IPAF	MNSIP 11	MNSIP 11	102

Most continued to have the same pattern of disease over time. 4 CTs returned to normal supporting the idea that OP has a good prognosis (Table 5). Rheumatoid Arthritis- 9% of patients with CTD had RA. The average age in our study was 66 and 83% were female. 3/6 had a UIP pattern similar to that which has been described in the literature [8]. None improved over the course of follow-up. Most continued to have the same pattern of disease over time. No patient with RA returned to normal on CT (Table 6). Idiopathic Pulmonary Fibrosis with Autoimmune Features: 6% of patients with CTD had IPAF, defined as a combination of findings of at least 2 of the following; clinical manifestations of CTD, positive serologies or specific chest CT pattern or pathology [9]. The average age in our study was 66, which was relatively

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old. 80% were female. Most patients had an NSIP pattern (60%). Chung found that UIP pattern was more common in the patients he studied [10] (Table 7). Mixed Connective Tissue Disease-5% of patients with CTD had MCTD. The average age in our study was 58, which was relatively young. 100% were female. There was a variable appearance on CT with no predilection for a specific pattern [11]. Most continued to have the same pattern of disease over time. One person's CT returned to normal (Table 8).

Table 8: Pattern of fibrosis and extent of disease on first and last CT scan and time between imaging in patients with mixed connective tissue disease.

	Initial	Last	Total Time (Months)
MCTD	POP 1	NORMAL	35
MCTD	NSOP 9	CNSIP 4	54
MCTD	MNSIP 7	MNSIP 8	142
MCTD	UIP 3	UIP 8	44

Sjogren's Disease-5% of patients with CTD had Sjogren's. The average age in our study was 66, which was relatively old. 100% were female. Most patients had a NSIP pattern. We did not observe the cysts that are characteristic of the disease. In Enomoto's study, many of the patients had a UIP pattern of disease [12]. The progression in our patients was variable but the pattern remained stable (Table 9).

Table 9: Pattern of fibrosis and extent of disease on first and last CT scan and time between imaging in patients with Sjogrens.

	Initial	Last	Total Time (Months)
SJOGRENS	CNSIP 6	CNSIP 2	19
SJOGRENS	NSOP 10	NSOP 4	23
SJOGRENS	MNSIP 4	MNSIP 5	67
SJOGRENS	MNSIP 11	FNSIP 12	69

Discussion

Ultimately, there are many types of CTD and they have variable radiographic presentations, which can evolve differently over time. The variability of the radiographic appearance within a specific type of CTD is interesting as is the overlap in appearance between different diseases. The OP pattern which is seen in many of the CTD is typically early and often resolves. In contrast the NSIP pattern is more likely to be persistent. Lung manifestations may be present prior to joint manifestations so it is important for rheumatologists to consider the lung in evaluation of patients with suspected connective tissue diseases. Further research is needed to determine the effect of immunosuppressant drugs on the evolution of findings on chest CT and determine if clinical parameters parallel radiographic appearance [13].

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