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Mixed Connective Tissue Disease: A Rare Disease with Many Faces

Chaïmaâ Zeroual*, Afaf Aallam, Safaa Mourabit, Mina Moudatir, Khadija Echchilali and Hassan Elkabli

Department of Internal Medicine and Geriatrics, Ibn Rochd University Hospital Center, Faculty of Medicine and Pharmacy of Casablanca, Morocco

***Corresponding Author**
Chaïmaâ Zeroual, Department of Internal Medicine and Geriatrics, Ibn Rochd University Hospital Center, Morocco.

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Abstract

Introduction: *Mixed connective tissue disease (MCTD) is a rare autoimmune disease characterized by overlapping clinical manifestations of several systemic connective tissue diseases and the presence of anti-U1RNP antibodies. This study aims to describe the clinical, immunological, and evolutionary features of patients with MCTD.*

Methods: *A retrospective descriptive study conducted over 5 years (2020–2024) in the internal medicine department of Ibn Rochd University Hospital Center in Casablanca, including 9 female patients meeting Kasukawa's criteria.*

Results: *All patients were female, with a mean age at diagnosis of 41.3 years. Raynaud's phenomenon was the most frequent inaugural sign. Pulmonary involvement was present in 66.6% of cases, with one-third of these patients exhibiting fibrotic changes. Anti-U1RNP antibodies were positive in 100% of patients. Evolution towards a differentiated connective tissue disease (lupus or systemic sclerosis) was observed in 77.7% of cases. The overall prognosis was favorable, despite one death related to a paraneoplastic syndrome.*

Conclusion: *MCTD remains a rare disease with variable clinical expression, requiring particular diagnostic vigilance. Early identification of evolving forms and multidisciplinary monitoring are essential to prevent complications and guide treatment*

Keywords: Mixed Connective Tissue Disease, Sharp's Syndrome, Anti-U1RNP, Ibn Rochd University Hospital Center, Casablanca

1. Introduction

Mixed connective tissue disease (MCTD) is a rare systemic autoimmune disorder characterized by an overlap of several connective tissue diseases, notably systemic lupus erythematosus and systemic sclerosis, in the presence of high-titer anti-U1-RNP antibodies [1-3]. Its clinical presentation is heterogeneous, frequently involving articular, muscular, cutaneous, pulmonary, or digestive manifestations, which often complicates and delays diagnosis [4]. Despite advances in the field, MCTD remains a clinical entity with still ill-defined boundaries, necessitating deeper insight to enhance patient management. The objective of this study is to report the experience of the Internal Medicine Department at Ibn Rochd University Hospital Center in Casablanca regarding this pathology over a five-year period.

2. Methods

This retrospective descriptive study was conducted from January 2020 to December 2024. The analysis included 9 female patients diagnosed with MCTD according to Kasukawa's criteria. Data were collected through a thorough review of the patients' medical records encompassing hospital admissions.

3. Results

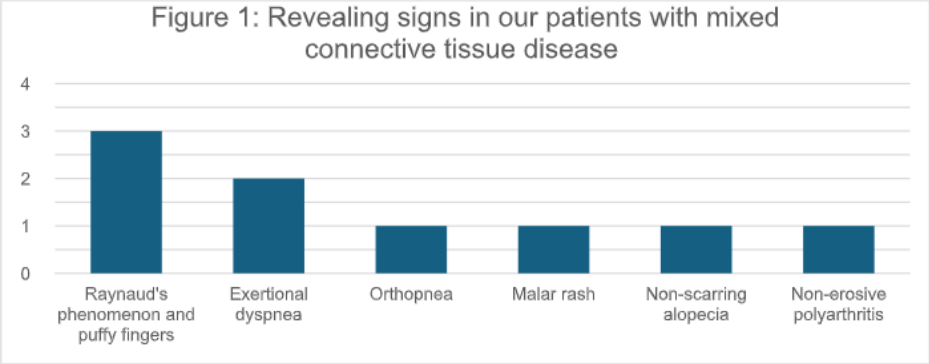
3.1. Demographic Data

Among the 1921 patients followed in internal medicine during the study period, 9 cases of MCTD were identified, representing a prevalence of 0.4%. All patients were female, with a mean age at diagnosis of 41.3 years.

3.2. Clinical Presentation

The most frequent inaugural presentation was Raynaud's phenomenon accompanied by puffy fingers (33.3%). Other notable clinical signs observed included (Figure 1):

- Exertional dyspnea (Grade 3 on the modified Medical Research Council (mMRC) scale): 2 patients
- Orthopnea with abundant pericardial effusion: 1 patient
- Malar rash (erythema in vespertilio): 1 patient
- Non-scarring alopecia: 1 patient
- Non-erosive polyarthritis: 1 patient



3.3. Associated Autoimmune Diseases

The presence of other autoimmune comorbidities was significant (Figure 2):

- Hashimoto's thyroiditis: 6 patients (66,6%)
- Sjögren's disease: 2 patients (22.2%)
- Immune thrombocytopenia: 1 patient (11,1%)
- Antiphospholipid syndrome (APS): 1 patient (11,1%)

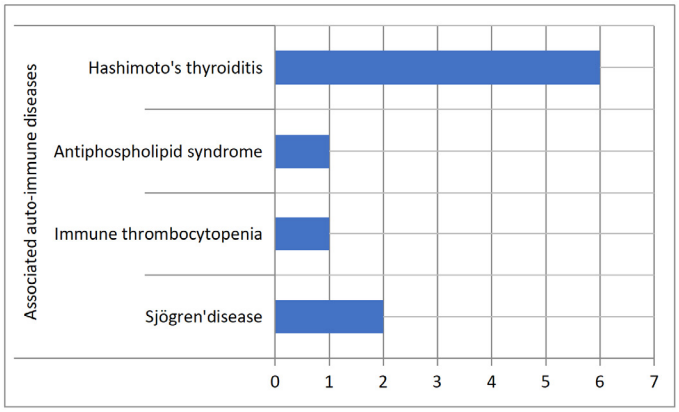
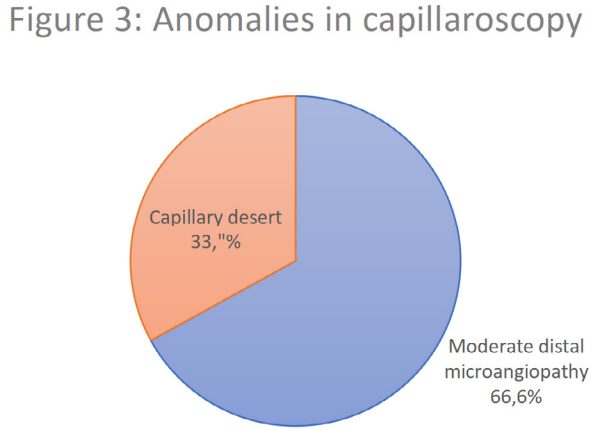


Figure 2 : Autoimmune Diseases Associated to Mixed Connective Tissue Diseases in Our Series

3.4. Ancillary Investigations

In capillaroscopy, all patients exhibited distal microangiopathy, with severe findings (e.g., capillary deserts, hemorrhages) in 33.3% of cases (Figure 3).



Immunologically, antinuclear antibodies (ANA) were positive in 100% of patients (titer ≥ 1/640). The immunofluorescence pattern was speckled in 66.6% and a mixed homogeneous and speckled pattern in 33.3% (Figure 4). Anti-U1RNP antibodies were positive in 100% of patients, with strong positivity noted in 33.3% (Figure 5).

Figure 4: The appearance of antinuclear antibodies in indirect immunofluorescence

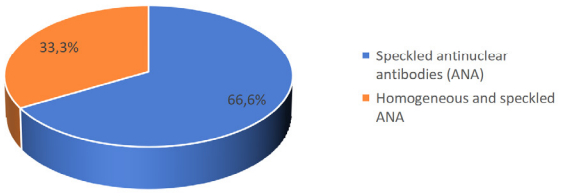
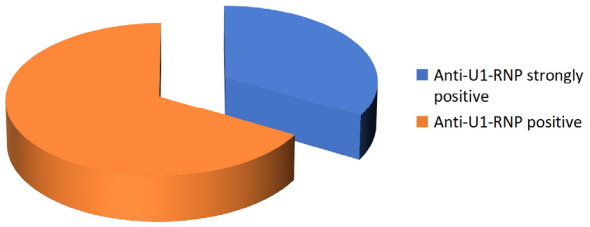


Figure 5: Qualitative profile of anti-U1RNP antibodies



3.5. Organ Involvement

8 patients presented with pulmonary hypertension (PHT) in echocardiogram (Figure 6). Whereas confirmed PHT was present in only 2 patients. Thoracic computed tomography scan revealed no involvement in 33.3% of cases, non-fibrosing interstitial lung disease in 33.3%, and pulmonary fibrosis in 33.3% (Figure 7). Pulmonary function tests indicated restrictive ventilatory defects in 22.2% and mixed ventilatory defects in 22.2%.

Figure 6: Number of patients presenting or not with pulmonary hypertension

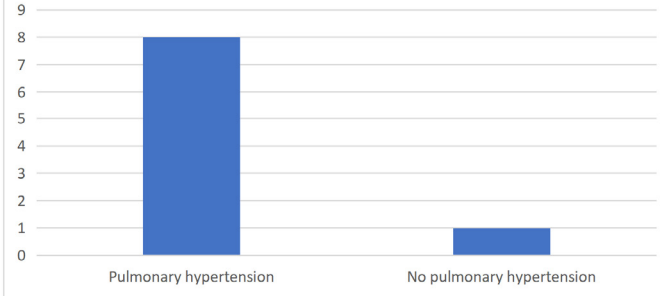
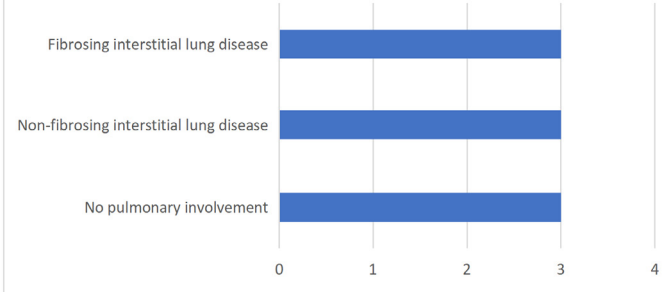


Figure 7: Anomalies revealed in thoracic computed tomography scan



3.6. Therapeutic Management

All patients received a calcium channel blocker. In addition, the following treatments were administered:

-Corticosteroids and mycophenolate mofetil: 55.5%

-Hydroxychloroquine: 44.4%

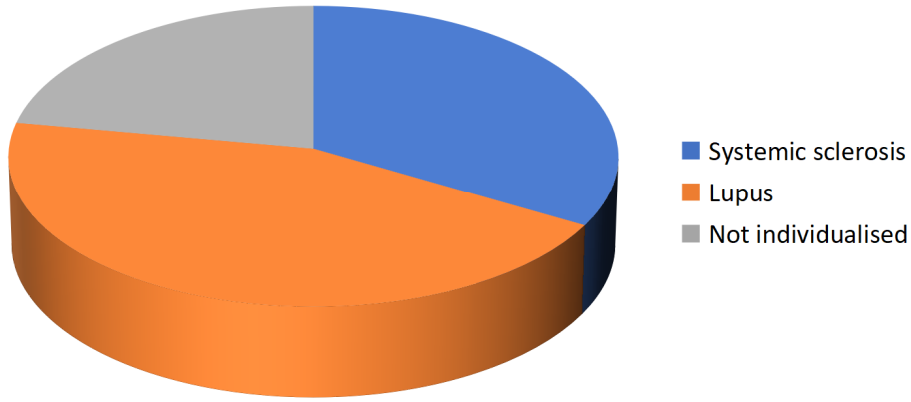
3.7. Evolution and Prognosis

The disease course demonstrated varied differentiation patterns (Figure 8):

- Differentiation towards systemic sclerosis: 33.3% (including one paraneoplastic case)
- Differentiation towards systemic lupus erythematosus: 44.4%
- Not individualized MCTD: 22.2%

The overall outcome was favorable in 88.8% of cases. Unfortunately, one patient (11.1%) succumbed to the disease, specifically due to a paraneoplastic form of systemic sclerosis.

Figure 8: Evolution of MCTD



4. Discussion

MCTD, also called Sharp's syndrome, is an autoimmune entity defined by the coexistence of symptoms belonging to several systemic connective tissue diseases (systemic lupus erythematosus, systemic sclerosis, polymyositis) and by the presence of anti-U1RNP antibodies. Diagnosis is based on criteria sets such as those by Sharp, Kasukawa, Alarcón-Segovia, Kahn and Tanaka (Table 1) [1,5- 8].

Criteria	Key Criteria	Clinical Features	Immunological Features	Diagnostic Requirements	Sensitivity / Specificity
Sharp Criteria [1]	Major criteria: severe myositis, pulmonary involvement (DLCO <70%, PAH, vascular lesions), Raynaud's phenomenon (RP) or esophageal hypomotility, edema of hands/sclerodactyly, anti-ENA antibodies ≥1:10,000 with anti-nRNP positive and anti-Sm negative	Myositis, RP, swollen hands, pulmonary involvement	High titer anti-U1-RNP antibody, anti-ENA positive, anti-Sm negative	4 major criteria + anti-RNP titer >1:4000; or 2 major + 2 minor + anti-nRNP ≥1:1000	Sensitivity 57.7%, Specificity 90%
Kahn Criteria [7]	Serological: Anti-nRNP >1:1600	RP, synovitis, myositis, swollen fingers	Anti-nRNP antibody titer >1:1600	Serological criterion + RP + ≥2 clinical criteria	Sensitivity 52.3%, Specificity 99.4%
Alarcón-Segovia Criteria [6]	Serological: Anti-nRNP >1:1600	Edema of hands, synovitis, myositis, RP, acrosclerosis	Anti-nRNP antibody titer >1:1600	Serological + ≥3 clinical criteria (including synovitis or myositis)	Sensitivity 69.4%, Specificity 99.4%
Kasukawa Criteria [5]	Common symptoms: RP, swollen fingers/hands, anti-nRNP positive	SLE-like (polyarthritis, rash, lymphadenopathy, pericarditis); SSc-like (sclerodactyly, ILD, esophageal dysmotility); PM-like (muscle weakness, elevated CPK, myogenic EMG)	Anti-nRNP positive	≥1 common symptom + anti-nRNP + ≥1 mixed symptom from at least two categories (SLE-like, SSc-like, PM-like)	Sensitivity 77.5%, Specificity 92.2%

Tanaka Criteria [8]	I. Common: RP, puffy fingers/swollen hands; II. Immunological: Anti-U1RNP positive; III. Characteristic organ: PAH, aseptic meningitis, trigeminal neuropathy; IV. Overlapping manifestations (SLE-like, SSc-like, PM/DM-like features)	Includes systemic features of SLE, systemic sclerosis, polymyositis	Anti-U1RNP positivity required	At least one common + immunological + one characteristic organ involvement OR one from overlapping manifestations in 2+ categories	Sensitivity 90.6%, Specificity 98.4%

Table 1 : The different diagnostic criteria for MCTD based on established classifications from the literature. Abbreviations: RP: Raynaud's Phenomenon ; Anti-nRNP: Anti-U1 ribonucleoprotein antibodies ; PAH: Pulmonary arterial hypertension ; SLE: Systemic lupus erythematosus ; SSc: Systemic sclerosis ; PM/DM: Polymyositis/Dermatomyositis ; DLCO: Diffusing capacity for carbon monoxide ; CPK: Creatine phosphokinase.

Although recognized since the 1970s , MCTD remains uncommon, representing less than 2% of systemic connective tissue diseases in most series . In our study, it accounted for 0.4% of patients followed in internal medicine, confirming its rarity. The female predominance is well-established: in the large cohort by Burdt et al. (n = 91), 92% of patients were women, as was the case in the Norwegian study by Gunnarsson et al. (n = 147), with 89% female patients [9,10]. Our series is consistent, with 100% female patients. The mean age at diagnosis generally ranges between 30 and 50 years [9,10]. In our series, the mean age at diagnosis was 41.3 years, falling within this range.

Raynaud's phenomenon is often the inaugural sign, reported in 80 to 100% of cases. In our study, it was present in one-third of patients at onset. It is frequently associated with capillaroscopic abnormalities, as we also observed in all of our patients. Severe forms (microangiopathy, capillary dropout) were present in 33.3%, comparable to what Cutolo et al. report in systemic connective tissue diseases with early vascular involvement [11].

Arthralgias and non-erosive polyarthritis occur in 50 to 80% of cases, often rheumatoid-like but without joint destruction [12]. In our cohort, only one patient (11%) presented with arthropathy. Malar rash (11%) and non-scarring alopecia (11%) are more characteristic manifestations of lupus, also found in our series.

The coexistence of autoimmune diseases is frequent. Autoimmune thyroiditis is found in about 30 to 40% of MCTD cases [13,14]. In our study, this proportion was even higher (66.6%), which might reflect a specificity of our population or a recruitment bias. Sjögren's syndrome is also reported in MCTD, found in 22.2% of our patients [15].

Antinuclear antibodies (ANA) positivity is constant in MCTD, generally at high titers (≥1/640), with a speckled or mixed pattern [16]. Our data confirm this tendency: all cases were positive, with 77.7% having a titer of 1/1280. The anti-U1RNP antibody is the central immunological marker [17]. It was strongly positive in all our patients, in line with Kasukawa's criteria. Other autoantibodies (anti-dsDNA, anti-Ro/SSA, anti-Scl70) may be transiently present but are not specific (Table 2) [18,19].

Autoantibody	Clinical/Diagnostic Notes
Anti-U1-RNP	Hallmark antibody; key diagnostic marker for MCTD
Antinuclear Antibody (ANA)	Positive ANA with speckled pattern common
Anti-Sm	Can develop over time; associated with overlapping autoimmune features
Rheumatoid Factor (RF)	Associated with arthritis features and sometimes with erosive arthritis
Anti-dsDNA	More typical of systemic lupus but seen in MCTD overlap patients
Anti-Ro/SSA	Seen variably; may indicate overlap with Sjögren's or lupus features
Anti-CCP	Linked to erosive arthritis in a subset of MCTD patients
Anti-PM-Scl	Suggests overlap with myositis or scleroderma components
Anti-Ku	Associated with overlap syndromes involving myositis and lung disease

Table 2: Clinical/Diagnostic Notes of Autoantibodies in MCTD

Pulmonary involvement is the main cause of death in MCTD. Pulmonary fibrosis (PF) is found in 20 to 40% of cases depending on the series, with a strong association to scleroderma-like progression [20]. In our study, one-third of patients already had PF at diagnosis, demonstrating the potential severity of respiratory involvement. Restrictive or mixed ventilatory defects, found in 44% of our patients, are also well described in pulmonary function tests of patients with MCTD.

Pulmonary arterial hypertension (PAH) affects 10 to 20% of patients in various series (up to 40% in advanced forms). PAH is the most serious life-threatening complication, making regular screening

for this condition crucial [21]. Its detection via echocardiography and confirmation by right heart catheterization is essential [22]. In our cohort, 22.2% of patients had confirmed PAH.

Prevalence of cardiac involvement varied from 13% to 65% in MCTD cases, and pericarditis is the most common cardiac diagnosis with a prevalence of 30% and 43% [23]. One of our patients presented with orthopnea and a large pericardial effusion, which is consistent. Neurological and renal involvements are rarer and were not found in our series.

A major feature of MCTD is its nosological instability. Several longitudinal studies show that about 30 to 70% of patients evolve over time toward a differentiated connective tissue disease, most often systemic lupus or systemic sclerosis [24,25]. In our series, 77.7% of patients had already evolved: 44.4% toward lupus, 33.3% toward systemic sclerosis (including one paraneoplastic case), and 22.2% remained undifferentiated. This progression suggests that MCTD could represent an intermediate or early state of other connective tissue diseases rather than a stable entity. This hypothesis is reinforced by the clinical, immunological, and therapeutic evolution observed over time.

Treatment for MCTD depends on the type of manifestations. Corticosteroids are widely used to control inflammatory phases, often combined with immunosuppressants (azathioprine, mycophenolate mofetil, methotrexate) depending on organ involvement [26]. In our study, 55.5% received corticosteroids and mycophenolate. Hydroxychloroquine is recommended for mild articular or cutaneous involvement [27].

For interstitial lung disease, particularly early or moderate forms, several studies have demonstrated the efficacy of mycophenolate mofetil and cyclophosphamide in stabilizing respiratory function and even improving functional parameters [28].

5. Conclusion

MCTD is a rare and complex autoimmune disorder that poses significant diagnostic challenges due to the absence of highly specific criteria. Enhancing the standardization of immunological and clinical assessment tools is essential to enable earlier detection. Physician's main goal remains improving patient monitoring and better anticipating potential complications. Looking ahead, ongoing research hold promise for more precise diagnostic methods and targeted therapies, offering hope for management of MCTD in the future.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in this study are in accordance with the ethical standards of the institutional and/or national research comittee(s). Written informed consent was obtained from the patients for publication of this case series.

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