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# Autoimmune Complexity: Hashimoto's Thyroiditis in Mixed Connective Tissue Disease - A Case Report

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**Abstract:**
Mixed Connective Tissue Disease (MCTD) is an autoimmune disease with the same clinical features as Rheumatoid Arthritis, Systemic Sclerosis, and Systemic Lupus Erythematosus. Its complexity and heterogeneous clinical presentation make diagnosis challenging. MCTD has been linked to one or more autoimmune diseases (ADs), including autoimmune thyroid disorders (AITD). Screening for additional autoimmune disorders is crucial to avert delays in the identification and management of these conditions, particularly in patients who continue to feel sick or who develop new non-specific symptoms.
**Case description:**
MCTD, Sjögren's syndrome, and systemic lupus erythematosus (SLE with cerebritis) were diagnosed in a 37-year-old woman six years earlier. Her diagnosis was established based on her clinical presentation, comprehensive diagnostic work-up, and adherence to diagnostic criteria.
She presented to the outpatient clinic with worsening fatigue, myalgia-like symptoms, a sensation of coldness, and increased gastrointestinal discomfort. The further evaluation confirmed a diagnosis of autoimmune thyroiditis, based on thyroid function test results indicating aberrant TSH, T3, and T4 levels and increased anti-thyroid peroxidase antibodies (anti-TPO). Thyroid ultrasonography result points to thyroiditis: There are no focal or cystic alterations in the small, smooth, and homogenous thyroid lobes. Ultimately, other possible differentials were ruled out.
**Conclusion:**
The intricacy of diagnosing mixed connective tissue disease (MCTD) and its correlation with various autoimmune disorders is underscored by this particular case. This underscores the importance of ongoing vigilance and comprehensive evaluation in patients with MCTD, as the early identification and management of coexisting autoimmune conditions are crucial for optimizing patient outcomes.
***Keywords: MCTD, Lupus Cerbritis, Sjögren's Syndrome, Hashimoto's Thyroiditis***

## Introduction:

"Mixed Connective Tissue Disease" (MCTD) is a rare autoimmune disease that first came into existence by Sharp et al. in 1972. Clinically, it shares many similarities with systemic lupus erythematosus (SLE), polymyositis (PM), and systemic sclerosis (SSc) in many ways. It is widely acknowledged that MCTD, which is linked to a particular autoantibody called anti-U1-Ribonucleoprotein (anti-U1RNP), should be regarded as a separate clinical entity as opposed to an overlap condition [1].
Despite its uncommon nature, varied manifestation, and multiple organ involvement, mortality was comparable

to that of the general population. [2, 3]

Although the pathophysiology of this condition is unclear, it appears to be multifactorial, the development of MCTD is genetically correlated with individuals with HLA-DR4; no such association was found with HLA-DR3 or -DR5, which have a significant connection with SLE patients and systemic sclerosis, accordingly. [1]

The autoantibody anti-U1RNP also referred to as anti-nRNP, targets the 70 kDa component of the U1 RNP complex, a protein that intracellularly influences mRNA maturation, and it typifies the disease [4,5]. Anti-U1RNP appears to have predictive value as well. A high titer of anti-U1RNP is linked to a lower frequency of neurological consequences and an occurrence of pulmonary hypertension. On the other hand, a prolonged remission of the condition is associated with its absence [6].

A common and catastrophic adverse consequence of connective tissue diseases (CTDs) is the development of pulmonary hypertension, which mostly affects patients with systemic lupus erythematosus (SLE), primary Sjogren's syndrome (pSS), mixed connective tissue disease (MCTD), and systemic sclerosis (SSc) [7].

Clinically, non-specific symptoms like fatigue, arthralgia, and low-grade fever are typical of MCTD patients; the skin is the first organ to be specifically affected. Skin involvement common to SLE and especially SSc, including Raynaud's Phenomenon (RP), puffy hands to sclerodactyly, acrosclerosis, calcinosis, ulcers, and digital necrosis, may be linked to MCTD [8].

In addition to inflammatory arthritis, which is often observed in the disorder's early stages, inflammatory myopathy is another prevalent clinical characteristic of MCTD. The hallmark electromyography changes, proximal weaknesses, and boosted blood concentrations of skeletal muscle enzymes are among the clinical manifestations of inflammatory myopathy [2,9].

Multiple organ involvement is one of the most important characteristics of MCTD; in about half of the patients, the most common symptom of gut involvement is gastroesophageal reflux disease (GERD), which manifests as heartburn and hypomotility. Hepatitis with an autoimmune component is less frequent [9,10].

Cardiopulmonary involvement is similarly widespread; in about 73% of patients, pulmonary involvement includes interstitial lung disease (ILD), pulmonary arterial hypertension, and pleural efflux. Nearly 90% of patients have a high prevalence of fibrotic Nonspecific Interstitial Pneumonia (NSIP) pattern on the High-Resolution Computed Tomography (HRCT) scan. [9,10]. As opposed to this, up to 40% of the patients experience pericarditis, which is the most prevalent kind of cardiac illness. Conduction abnormalities, accelerated atherosclerosis, myocarditis, pericardial effusion, and mitral valve prolapses can also exist [10].

Trigeminal neuralgia is the most common central nervous system symptom; other potential symptoms include convulsions, headaches, nuchal rigidity, aseptic meningitis, and sensorineural hearing loss. The other manifestations are usually mild and include depression and cognitive impairment. Similar to SLE, there is a chance of encephalitis, psychosis, and seizures [9,10].

In contrast, 15–25% of patients with MCTD experience renal involvement. For the most part, patients have no symptoms. The most typical diagnosis is membranous nephropathy. Scleroderma renal crisis and other kidney-related symptoms common to SLE and SSc are also documented. Periodic kidney disease (CKD), which frequently necessitates dialysis, and severe morbidity are all possible outcomes of nephropathy [9,10].

Hematologic manifestations can also occur in MCTD patients. As also noted for SLE, the most prevalent ones are leukopenia, autoimmune thrombocytopenia, and hemolytic anemia.

Based on the four available historical classification criteria, MCTD has been categorized. The sets with the highest specificity are those suggested by Kahn and Alarcón-Segovia-Villareal (both 99.4%) [11]. MCTD has been categorized by the most recent historical classification criteria. Alarcón-Segovia-Villareal and Kahn's (both 99.4%) specificity sets rank among the best; furthermore, an updated suite of standards for diagnosis was presented in 2019[2,11].

**Table 1**

Diagnostic Criteria for Mixed Connective Tissue Disease (2019): Guidelines from the Japan Research Committee of the Ministry of Health, Labor, and Welfare for Systemic Autoimmune Diseases"

| |
|---|
| I. **Common clinical manifestations** |
| 1. Raynaud's phenomenon |
| 2. Puffy fingers and/or swollen hands |
| **II. Immunological indicators** |
| Positive anti-U1 ribonucleoprotein antibody |
| **III. Characteristics of specific organ involvement** |
| 1. Pulmonary Arterial Hypertension |
| 2. Aseptic meningitis |
| 3. Trigeminal neuropathy |
| **IV. Overlapping Clinical Features** |
| ***A. Systemic lupus erythematosus-like manifestations*** |
| 1. Polyarthritis |
| 2. Lymphadenopathy |
| 3. Malar rash |
| 4. Pericarditis or pleuritic |
| 5. Leukopenia (4,000/μL or less) or Thrombocytopenia (100,000/μL or less) |
| ***B. Systemic sclerosis-like Features*** |
| 1. Sclerodactyly |
| 2. Interstitial Lung Disease |
| 3. Oesophageal Dysmotility or Dilatation |
| ***C. Polymyositis/Dermatomyositis- Clinical Like Manifestations*** |

| |
|---|
| 1. Muscle Weakness |
| 2. Elevated Levels of Myogenic Enzymes |
| 3. Myogenic abnormalities on electromyogram |

*Diagnosis: Patients who satisfy the following criteria are diagnosed with Mixed Connective Tissue Disease (MCTD): Option 1: Having a minimum of one immunological manifestation, one common manifestation, and a minimum of one distinctive organ involvement.*
*Choice 2: Having a minimum of one immunological manifestation, one common manifestation, and a minimum of one feature from each of the three categories (A, B, and C) with overlapping manifestations*
It is noteworthy that numerous studies conducted thus far have established a correlation between autoimmune rheumatic disorders (ARD) and autoimmune thyroid disease (ATD). The two autoimmune thyroid diseases that overlapped the most were mixed connective tissue disease (MCTD) and Sjögren's syndrome (SS), accounting for 10% and 24% of cases, respectively [12,13].
It is common for autoimmune thyroid disorders, such as Hashimoto's thyroiditis (HT) and Graves' disease (GD), to overlap with organ-specific disorders such as pernicious anemia, systemic or ocular myasthenia, Addison's disease, immune thrombocytopenia, vitiligo, and type 1 (insulin-dependent) diabetes mellitus (IDDM). Information about HT or GD's overlap with systemic autoimmune disorders is comparatively scarcer. The correlation between thyroid disorders and Sjogren's syndrome (SS), rheumatoid arthritis (RA), systemic sclerosis (SSc), and systemic lupus erythematosus (SLE) has not been well-documented in cohort studies or case reports [12,13].

**Case description:**
A woman in her 37s came with a variety of symptoms that started about six years ago. She initially had neck pain, headaches that resembled migraines, and overall exhaustion. She also reported swelling, stiffness in the mornings in the phalanges and interphalangeal joints, and pain in the bones and joints. The patient reported petechial skin lesions on several body parts and increased sensitivity to cold, which caused her fingers to turn white, especially during cold weather. She was referred to a rheumatologist by an orthopedic surgeon, but she did not find the diagnosis convincing. Even after taking over-the-counter pain relievers, her symptoms persisted. One year later, she started having blackouts associated with loss of consciousness, which were preceded by left-sided numbness. Additionally, she began to experience symptoms such as spontaneous tooth loss, frequent dental caries, and dry mouth and eyes. She also developed heartburn, was diagnosed with GERD, and had growing swallowing difficulties. Based on the diagnostic criteria. She was diagnosed with Mixed Connective Tissue Disease (MCTD) by a rheumatologist, which encompasses both Sjögren's syndrome and Systemic Lupus Erythematosus (SLE) with cerebritis. ***(Table 1)***.
Initial laboratory tests showed normal CBC, LFT, KFT, and lipid profiles. However, subsequent tests indicated features of iron deficiency anemia (***Table 2).***
**Table 2:** Hematology and metabolic work-up

| Date | Investigation | Patient result | Normal range |
|---|---|---|---|
| 08/05/2018 | ***Full blood count*** | | |
| | WBC | 7.05 X $10^9$ /L | (4.5-10) X $10^9$ /L |
| | Neutrophils% | 70.6% | (40- 75)% |
| | Lymphocytes % | 22% | (20-45)% |
| | Monocytes % | 6.4 % | (2- 10)% |

| | | | |
|---|---|---|---|
| | Eosinophil % | 0.9% | (1- 6)% |
| | Basophils % | 0.1% | (0 -1 )% |
| | HGB | 13 g/dl | (11.5- 16.5) g/dl |
| | RBC | 5.3 X $10^9$ /L | (3.8-5.8) X $10^9$ /L |
| | HCT | 40.5% | (37- 47)% |
| | MCV | 76.4 fl | (76-96) fl |
| | MCH | 24.5 pg | (27-32) |
| | MCHC | 32.1 g/dl | (30-35) |
| | Platelets | 244 X $10^9$ /L | (150-400) X $10^9$ /L |
| | RDW | 11.2 fl | (7.4- 10.9) fl |
| 08/05/2018 | ***Liver panel*** | | |
| | Bilirubin total | 7,4 Umol/L | (0-17) |
| | Alkaline phosphatase | 69 U/L | (50-137) |
| | ALT | 11.7 U/L | (10-50) |
| | AST | 15,3 U/L | (15-37) |
| | Total Protein | 85.3 | (64-82) |
| | Albumin | 41.8 | (34- 50) |
| 08/05/2018 | ***Renal Panel*** | | |
| | Sodium | 137 mmol/L | (135- 153) mmol/L |
| | Potassium | 4.47 mmol/L | (3.5-5.3) mmol/L |
| | BUN | 2.3 mmol/L | (2.6-6.4) mmol/L |
| | Creatinine | 52 Umol/L | (50-115) Umol |
| 08/05/2018 | ***Lipid Profile*** | | |
| | Cholesterol | 5.26 mmol/ | (3.28- 5.57) mmol/L |
| | Triglycerides | 1.09 mmol/L | (0.8- 2.2) mmol/L |
| | HDL-Cholesterol | 1.15 mmol/L | (0.8-1.8) mmol/L |
| | LD-Cholesterol | 4 mmol/L | (1.8- 4.9) mmol/L |
| 18/02/2024 | ***Full blood count*** | | |
| | | | |
| | WBC | 5.05 X $10^9$ /L | (4.5-10) X $10^9$ /L |
| | Neutrophils% | 67.3% | (40- 75)% |
| | Lymphocytes % | 19.3% | (20-45)% |
| | Monocytes % | 12.1 % | (2- 10)% |
| | Eosinophil % | 0.9% | (1- 6)% |
| | Basophils % | 0.1% | (0 -1 )% |
| | HGB | ***9.5*** g/dl | (11.5- 16.5) g/dl |
| | RBC | 4.34 X $10^9$ /L | (3.8-5.8) X $10^9$ /L |
| | HCT | **30.3%** | (37- 47)% |
| | MCV | ***69.8*** fl | (76-96) fl |
| | MCH | ***21.9*** pg | (27-32) |
| | MCHC | 31.4 g/dl | (30-35) |
| | Platelets | 269 X $10^9$ /L | (150-400) X $10^9$ /L |
| | RDW | 11.2 fl | (7.4- 10.9) fl |

| | | | |
|---|---|---|---|
| | S iron | ***3.60*** mm/l | (8.26- 26.85) mmol/l |

Her immune profile was consistently abnormal, with a positive ANA of 130.11 U/ml (positive > 55 U/ml) and a titer of 1:320 (May 15, 2018), an intermediate anti-dsDNA level of 31.2 IU/ml (intermediate: 27-35 IU/ml), and abnormal anti-CCP antibodies. Various inflammatory markers and immunology tests also displayed abnormalities at different times (***Table 3).***

**Table 3:** Laboratory work-up; serology and immunology

| Date | Investigations | Patient Result | Normal Values |
|---|---|---|---|
| 12/12/2017 | CRP | 24 mg/dl | Negative < 6 mg/dl |
| | RF | < 12 IU/ml | |
| | ESR | 40 mm/hr. | 2-15 mm/hr. |
| | VIT D3 | 35 ng/ml | Sufficient = 30-100 |
| | ANA | 130.11 U/ml | Positive=> 55 U/ml<br>Negative < 40<br>Equivocal= 40-55 |
| | Anti-CCP antibodies | 6.12 U/ml | Positive = > 17 U/ml |
| 15/05/2018 | Anti-SM | 42 U/ml | Positive > 1.4 U/ml |
| | Anti SSA(RO) | 112 AU/ml | Positive > 6 U/ml |
| | Anti SSB(LA) | 74 AU/ml | Positive > 6 U/ml |
| | ANA | 1/320 | |
| | Ani DNA (ABS) | Negative | |
| | C3 | 1.03 g/L | (0.9- 1.8) g/L |
| | C4 | 0.131 g/l | (0.1- 0.4) g/L |
| | TFT | FT3 = 4.16 pmol/L<br>FT4 = 18.69 pmol/L<br>TSH = 2.44 mlu/L | FT3 = (3.1- 6.8) pmol/L<br>FT4 = (12- 22) pmol/L<br>TSH = (0.27-4.2) mlu/L |
| | Virology | Anti-HCV screening = negative<br>HBsAg = negative<br>HIV = negative | |
| 03/10/2018 | Anti-ds DNA abs | 31.2 IU/ml | Positive > 35 IU/ml<br>Intermediate 27-35 IU/ml |
| | Anti-RNP Abs | > 643.8 CU | Positive > 20 CU |
| | Anti-Smith Abs | 235.1 CU | Positive > 20 CU |
| | Anti SSA(RO | > 1374.8 CU | Positive > 20 CU |
| | Anti-SSB (LA) | 30.5 CU | Positive > 20 CU |
| 10/10/2018 | Anti U1 RNP | <0.9* | |
| | Anti Sm | > 8* | |
| | Anti-Centromere B | <0.9 * | Positive >1.2 |
| | Anti Scl-70 | < 0.9 * | Positive >1.2 |
| | Anti Jo-1 | < 0.9* | Positive >1.2 |
| | Anti SSA(RO | 1.1* | Positive >1.2 |
| | Anti SSB (LA) | > 8* | Positive >1.2 |

| | | | |
|---|---|---|---|
| 18/02/2024 | ANA | 1/1280* | |
| | Anti-ds DNA | Positive*/ speculated | |
| | Anti-Sm | Positive* | |
| | Anti RNP | Positive* | |
| | Anti SSA(RO | Positive* | |
| | Anti SSB (LA) | Negative | |
| | Anti-Centromere B | Negative | |
| | Anti Scl-70 | Negative | |
| | AntiPM-Sc-100 | Negative | |
| | Anti-TPO | Positive | |
| | Ant-TSH | Positive | |
| 18/02/2024 | TFT | T3=<br>T4=<br>TSH= | |
| | | | |

*= (patient on immunosuppressive treatment)

Bilateral white matter hyper-intense foci were seen on T2/FLAIR during a brain MRI. Six months later, a follow-up whole-spine brain MRI revealed a small enlargement of these foci but no new abnormalities or indications of spinal cord involvement. Rather than being indicative of ischemia or demyelinating illness, the features suggested vasculitis. ***(Table 4)***

**Table 4:** Diagnostic images

| Date | Diagnostic Image | Finding |
|---|---|---|
| 14/05/2018 | Brain MRI | White matter hyper-intense foci bilateral seen in T2/Flair |
| 11/11/2018 | Brain & Whole Spine MRI with contrast | The previously, white matter hyper-intense foci bilateral seen in T2/Flair, are slightly increased in size, otherwise, no significant interval changes could be appreciated in numbers, and no restricted diffusion and no abnormal enhancement post-contrast were seen. No newly developed abnormality was seen and no evidence of spinal cord involvement and features are suggestive of vasculitis rather than ischemia or demyelinating disease. |
| 27/08/2020 | MRI Brain without contrast | Nearly stationary course disease status regarding, the white matter hyper-intense foci on T2/Flair-W1, imaging features and provided the history of SLE, are suggestive of vasculitis (mostly) rather than ischemic or demyelinating disease, a newly developed abnormality seen |
| 27/02/2024 | Echocardiography | Normal systolic function and normal LV size EF = 60%, NO RWMA<br>The aortic root and mitral valve are normal, with no lesions, AV and RV are normal in size and function, TR and RVSP are equal to 14 mmHg, and there is no pericardial effusion. |
| 27/02/2024 | Thyroid U/S | Both thyroid lobes are relatively small in size with smooth surface contour and a homogenous stromal pattern with no evidence of focal mass or cystic changes within. |

The patient was taking 200 mg of hydroxyl-chloroquine twice daily, a dose of 100 mg of azathioprine daily, and 1000 mg of Levetiracetam daily. In addition to valsartan 80 mg once a day is prescribed for hypertension.

Her condition remained stable and she was seizure-free until her last visit to our clinic, where she presented with increased fatigability, myalgia-like symptoms, cold intolerance, hair loss, and greater gastrointestinal discomfort.

Her vitals were examined and found normal, except for a 160/100 blood pressure reading. A systematic examination was also normal. Routine workup, including immunology tests, was repeated, revealing hypothyroidism with TSH, T3, and T4 levels indicating this condition. Additionally, thyroid autoantibodies were positive for Anti-TPO and Anti-TSH receptors. (***Table 2).***

Thyroid ultrasound showed features of thyroiditis: both thyroid lobes were relatively small with a smooth surface contour and homogenous stromal pattern, with no focal masses or cystic changes (***Table 4)***. The patient was prescribed levothyroxine 50 mcg daily in addition to her previous medications. The dosage was gradually adjusted based on clinical and hormone levels. She showed both clinical and biochemical improvement and was scheduled for follow-up at six-month intervals.

**Discussion:**

The development of anti-thyroid antibodies that target thyroid tissue and cause progressive fibrosis is a hallmark of Hashimoto thyroiditis also referred to as chronic lymphocytic thyroiditis (CLT). The condition is often not identified until much later in its course. It is associated with several non-thyroidal autoimmune diseases (NTADs), with the majority of women receiving a diagnosis between the ages of 30 and 50 [14]. Six years earlier, our 42-year-old patient was diagnosed with mixed connective tissue disease.

Interestingly, patients presented with biochemical features of hypothyroidism, with lymphocyte infiltration resulting in fibrosis as a typical feature [14]. Similar to our case, the US showed features of thyroiditis; both thyroid lobes are relatively small in size with a smooth surface contour.

Numerous studies have revealed a connection between thyroid and connective tissue disorders. Additionally, autoimmune hypothyroidism is frequently associated with rheumatologic symptoms like arthritis, arthralgia, and muscle soreness [15].

It is, however, common for autoimmune thyroiditis to occur in conjunction with other autoimmune conditions, such as mixed connective tissue disease, which is comparable to how our case is presented clinically. Approximately 20% to 50% of cases have anti-thyroglobulin (anti-TG) antibodies, whereas 90% to 95% have anti-thyroid peroxidase (anti-TPO) antibodies [16].

Patients with autoimmune thyroiditis frequently have positive antinuclear antibody (ANA) test results; these results are especially common when other autoimmune diseases are present. Even without overlapping autoimmune or connective tissue diseases (CTD), this could explain the high ANA levels in this case, despite the patient undergoing immunosuppressive treatment. Consequently, there were no clinical signs indicating disease activity [16]. ***(Table 3)***

Recent evidence suggests that arthritis can occur within the context of connective tissue diseases (CTDs) and may frequently co-occur with conditions previously considered classic organ-specific diseases. Additionally, autoimmune thyroiditis is linked to serology-negative arthritis that mimics rheumatoid arthritis (RA) but has a non-erosive phenotype, even in the absence of hypothyroidism or overlap with systemic autoimmune disorders [16]. This presentation can be linked to mixed connective tissue diseases and may obscure the diagnosis of thyroiditis.

Autoimmune thyroiditis is frequently associated with gastric disorders, affecting 10% to 40% of patients [17]. In approximately 40% of these cases, it is linked to autoimmune gastritis, which presents as chronic autoimmune gastritis and can lead to impaired production of hydrochloric acid and intrinsic factors [14]. Hypochlorhydria-dependent iron deficiency anemia may arise from this impairment, with the potential to progress to pernicious anemia and severe gastric atrophy [18]. Such manifestations might explain the gastrointestinal symptoms observed in this patient. Her negative results for anti-Centromere B, anti-Scl-70, and anti-PM-Scl-100 antibody tests ruled out the possibility that she had developed systemic sclerosis as a component of mixed connective tissue disease (MCTD) ***Table 3*** [19]. Additionally, echocardiography revealed no evidence of associated pulmonary hypertension, ruling out this possibility ***Table 4*** [20].

**Conclusion:**

The complexity of the diagnosis, the clinical challenges involved in addressing MCTD, and the fact that it can coexist with several autoimmune disorders are all highlighted by this case. It is essential for handling patients with MCTD with ongoing attention, thorough assessment, and proactive screening for other autoimmune disorders. By employing such strategies to improve treatment outcomes and diagnostic precision, healthcare providers can improve the quality of life for patients suffering from this complicated autoimmune disease.

The co-occurrence of Hashimoto thyroiditis with MCTD underscores the necessity for vigilant screening for additional autoimmune disorders in patients who remain symptomatic despite ongoing treatment. This case highlights the importance of recognizing and diagnosing overlapping autoimmune conditions to ensure comprehensive management and improve patient outcomes. An interdisciplinary approach to managing patients with multiple autoimmune disorders requires a coordinated multidisciplinary approach involving rheumatologists, endocrinologists, and other specialists.

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