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# Mixed connective tissue disease presenting as atrial fibrillation, fever, lymphadenopathy, and pericardial effusion

Jacob Mathew Jr., Tanner Kim, Timilyn Nunu, Jay Jahanmir

## ABSTRACT

**Introduction: Mixed connective tissue disease (MCTD) is a poorly understood rheumatologic condition that presents with clinical symptoms related to the underlying presence of distinct overlapping autoimmune conditions. Patients can be identified by the presence of a shared antibody to the U1 small nuclear ribonucleoprotein autoantigen. While the condition is considered incurable, prognosis is relatively good with most patients responding well to glucocorticoids. We report a case in which a patient presented with multiple nonspecific symptoms but was found to have multiple organ involvement that ultimately was tied to MCTD. Case Report: We report a 48-year-old male admitted with multiple nonspecific symptoms who was found to have atrial fibrillation, pericardial effusion, pleural effusions, diffuse lymphadenopathy and among other lab abnormalities, pancytopenia and various positive rheumatologic seromarkers. Extensive diagnostic workup led to a diagnosis of mixed connective tissue disease. Treatment with weight-based steroids led to a significant improvement of his symptoms. Conclusion: Mixed connective tissue disease (MCTD) is an autoimmune condition affecting almost every major organ of the body, defined by the presence of overlapping features from other connective tissue diseases. The use of available classification criteria and newly available biomarkers can assist in earlier diagnosis. While the condition is considered incurable, prognosis is good with use of glucocorticoid therapy. This case highlights the need to keep heightened suspicion for entities such as MCTD in patients who have various symptoms that may fit multiple distinct autoimmune conditions.**

**Keywords: Mixed connective tissue disease (MCTD), Rheumatology, Reactive lymphadenopathy**

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## INTRODUCTION

Mixed connective tissue disease (MCTD) represents a distinct disease of overlapping autoimmune conditions that often exist with antibodies targeted towards the U1 small nuclear ribonucleoprotein autoantigen. Symptoms are wide-ranging and include Raynaud's phenomenon, swollen fingers, erosive arthritis, subcutaneous nodules,

along with pulmonary and central nervous system involvement. With expanding knowledge into the role anti-U1RNP plays in the pathophysiology of the condition, providers are able to diagnose the condition more easily than before with serologic testing. While the condition is considered incurable, prognosis is relatively good with most patients responding well to glucocorticoids.

## CASE REPORT

A 48-year old African-American male was admitted to the hospital by the psychiatry service because of an episode of tachypnea, tachycardia, and atrial fibrillation.

Five days prior, he was evaluated in our institution's emergency room for a productive cough with fevers. A chest radiograph was performed and suggestive of pneumonia and a fourteen day course of oral levofloxacin was administered. He was on day-5 of antibiotic therapy when a friend brought him in after he had an argument with his mother, which subsequently led him to tell his friend that he would overdose on sleeping medications.

Review of systems was notable for a dry cough, pleuritic chest pain, fever, and chills for the past two weeks. He denied homicidal ideations or hallucinations.

Past medical history of the patient was obtained from outside hospital records as he was new to our institution. It showed a history of inflammatory skin rash treated with clobetasol cream, essential hypertension, Mobitz type I heart block, peripheral neuropathy, anemia of chronic inflammation, polyarthralgias, peripheral neuropathy of uncertain etiology, major depressive disorder, bipolar disorder, leukopenia with a reported normal bone marrow biopsy but otherwise unknown etiology, and impotence.

He was single, born in Chicago, and raised in Atlanta. He joined the Navy for three years, but was medically discharged for depression. He is currently unemployed and recently moved to Hawaii from Atlanta three months prior to his current hospitalization. He denied any tobacco or alcohol use, but did have a history of illicit drug use in 3–4 years ago with cocaine and marijuana. His family history was not significant for cancers or rheumatologic diseases. He had multiple allergies with uncertain reactions to include amoxicillin, sulfa, and atenolol.

Per report, vital signs were stable. Physical examination was notable for a cachectic African-American male who appeared older than his stated age. Scalp revealed a receding hair line, and other than a facial tattoo, his head and neck exam was unremarkable. No murmurs were auscultated and he was in regular rhythm. Pulmonary evaluation disclosed no rales or rhonchi. While he appeared quite thin, he did not have evidence of muscle atrophy. No rashes were present.

After evaluation, he was ultimately admitted to the psychiatric ward for suicidal ideation.

The following day, the patient suddenly became short of breath and tachypneic at a rate of 30–40 breaths per minute. The blood pressure was 128/89 mmHg, the heart rate was 138 bpm, and the oxygen saturation was 95% on room air. A rapid response team was called, and the patient was discovered to be in atrial fibrillation with rapid ventricular response. He was given a single dose of metoprolol 5 mg IV push and then transferred to the emergency department for further evaluation where Internal Medicine was eventually consulted.

Upon our services evaluation, the patient complained of 6/10 pleuritic chest pain, fatigue, and diffuse myalgia. He had chronic back and joint pain but noted that his current joint pain was much worse than baseline. The pain had worsened in both his knees over the past several weeks.

The patient was not taking any medications at the time other than the prescribed levofloxacin.

On examination, the patient was in no acute distress. He took short shallow breaths, and had a persistent dry cough. Otherwise, the patient was still due to the diffuse muscle and joint pain associated with moving. Any contact with his skin, such as with a stethoscope, caused him pain. The blood pressure was 141/97 mmHg, the pulse was 100 beats per minute, the respiratory rate was 20 per minute, the oxygen saturation was 95% on room air, and his BMI was 23.3. The patient had alopecia with a large tattoo over the top of his head. The jugular veins were not distended with the patient sitting at an incline. There were diminished breath sounds in the lower left lobe with no crackles, rales or rhonchi. Heart sounds were normal, with no murmurs, rubs or gallops. No cervical or axillary lymphadenopathy was palpable. The abdomen was non-distended and non-tender to palpation. Extremities revealed no edema or lesions, but he did display diffuse tenderness to palpation over the muscles and joints with evidence of swelling in both knees, elbows, and the metacarpal phalangeal joints of both upper extremities. He had full passive and active range of motion but did display pain with movement, with 5/5 strength in all extremities. The remainder of the exam was normal.

While in the emergency department, telemetry revealed that his atrial fibrillation had converted to normal sinus rhythm. EKG confirmed these findings.

The complete blood count revealed hemoglobin of 9.6 g/dL, hematocrit of 28.7%, white blood cells of $4.7x10^9$/L, and platelets of $289x10^9$/L. The MCV was 86.7 fL, and differential demonstrated 2% bands and 5% lymphocytes (normal: 22–44%). Erythrocyte sedimentation rate and C-reactive protein were elevated at 89 mm/hour and 13.82 mg/dL, respectively. Venous blood gases demonstrated a pH of 7.44, $pCO_2$ of 32 mmHg, and bicarbonate of 21.9 mEq/L. Coagulation studies and urinalysis were within normal limits.

A chest radiograph was performed to evaluate the patient's worsening tachypnea and pleuritic chest pain (Figure 1). Left greater than right pleural effusions were noted. There were no consolidations or opacifications appreciated. The cardiac silhouette was also enlarged, and surgical clips were seen in the left axilla.

The patient's clinical picture was concerning for a worsening infectious process, however, we could not rule out an underlying malignant vs. inflammatory process. He was admitted to the medicine service and started on IV vancomycin 1500 mg in addition to continuation of IV levofloxacin 750 mg. Rheumatologic workup included a positive ANA, SSA-A/B and anti-RNP. While this suggested a possible rheumatologic diagnosis, starting high dose steroids in a patient with an underlying infectious condition could worsen his clinical status. As a result, we focused on ruling out infection and malignancy before considering steroids.

Upon admission, additional imaging was obtained given the concerning chest X-ray findings. A chest CT scan without contrast was performed to evaluate the enlarged cardiac silhouette for cardiomyopathy or pericardial effusion, as well as evaluate the pleural effusion and possible loculations (Figure 2). Computed tomography scan demonstrated a large pericardial effusion. Moderately sized bilateral pleural effusion, with left greater than right, was observed with adjacent airspace disease suggestive of atelectasis. There was also complete collapse of the left lower lobe. A surgical clip and multiple enlarged left axillary lymph nodes were also present, with the largest measuring 2.3x1.9 cm a focal mass measuring 1.4x1.3 cm adjacent to the spleen was also observed (Figure 3).

The diffuse lymphadenopathy noted on imaging was concerning for malignancy, rheumatologic disease, or an infectious process. Given his adenopathy and pancytopenia, infectious causes to include tuberculosis and HIV were considered. HIV antibody and RNA viral load were negative. Pulmonary medicine was consulted and performed a bronchoalveolar lavage, which did not demonstrate acid-fast bacilli on fluorochrome stain. To investigate the adenopathy further, a PET-CT scan was obtained which demonstrated diffuse hypermetabolic lymph nodes in the mediastinum, bilateral axilla, supraclavicular spaces, spleen, iliac, and inguinal regions. ENT was consulted and performed an excisional lymph node biopsy of the largest palpable axillary node, which showed mature lymphocytes most consistent with benign or reactive lymphoid tissue.

The patient continued to be tachycardic and tachypneic. The computed tomography findings of pericardial effusion were further investigated. Pericardiocentesis was not pursued as he did not exhibit jugular venous distension, hypotension, or positive pulsus paradoxus (measured at 11 mmHg at bedside). A transthoracic echocardiogram revealed a moderately sized pericardial effusion with mild left ventricular wall thickness, which did not appear to be causing significant tamponade. Left ventricular size was normal, and no valve abnormalities were observed. For further evaluation, a right heart catheterization was performed, demonstrating a pulmonary artery pressure of 26/14 mmHg cardiac output of 6.8 ml/min. Again, no tamponade physiology was noted based on hemodynamics.

The patient remained persistently tachycardic and tachypneic throughout the coming days. Blood cultures drawn while the patient was in the emergency department remained negative after four days. MRSA nasal swab was negative. Given the initial chest imaging that showed bilateral effusions, a therapeutic and diagnostic thoracentesis was performed and 1.1 L of pleural fluid was removed from the left pleural space. Immediate follow-up portable chest X-ray demonstrated no evidence of pneumothorax and expected resolution of the left pleural effusion. Analysis of the fluid revealed an exudative process, with negative gram stain and cytology. However, the patient still remained tachycardia and tachypnea, despite the thoracentesis. A repeat chest radiograph demonstrated recurrence of the left sided pleural effusion.

After seven days of broad spectrum antibiotics and all cultures remaining negative, we ruled out an infectious cause of bacterial origin. HIV antibodies and RNA load were negative. Viral cultures were negative.

With infectious causes being ruled out, we consulted hematology to determine the risk for underlying malignancy given the benign biopsy results. We were able to obtain records from a prior civilian hospitalization over one year ago which showed similar sized adenopathy. Due to the chronicity of the lymphadenopathy and lack of significant change, the findings were considered to be most likely secondary to a chronic inflammatory condition rather than malignant.

With low suspicion for an infectious or malignant process, we focused on rheumatologic conditions. Given his multitude of symptoms that fit different clinical entities (i.e., lupus, scleroderma, etc.) and positive rheumatologic work-up, we suspected that the patient had a chronic, undiagnosed condition known as mixed connective tissue disease. A trial of weight-based steroids was initiated with prednisone 80 mg orally. Within 24 hours, the patient had symptomatically improved and we noted resolution in his chronic sinus tachycardia and tachypnea. After a week, he had begun to regain strength and was tapered to 60 mg per day. With his improvement, he was eventually discharged to a rehabilitation facility with a follow-up scheduled for a local rheumatologist. He has not been readmitted to this or any neighboring island medical facility since admission and his condition remains under the care of a civilian rheumatologist.

## DISCUSSION

Mixed connective tissue disease (MCTD), is an autoimmune condition affecting almost every major organ of the body, defined by the presence of overlapping features from five major connective tissue diseases: systemic lupus erythematosus, scleroderma, polymyositis, dermatomyositis, and rheumatoid arthritis [1, 2]. It was first discovered in 1972 by Sharp et al. in patients who displayed symptoms of various connective tissue diseases

along with an antibody against ribonucleoprotein antigen (RNP) [3]. Additional features such as alopecia, leukopenia, anemia, and lymphadenopathy have also been reported, all of which were seen in our patient [4]. The exact prevalence is unknown, but is most common between the ages of 4–80 years and has a high female predominance (80%) [3]. In a majority of patients, symptoms will progress in different disease episodes rather than all present on initial clinical evaluation [3].

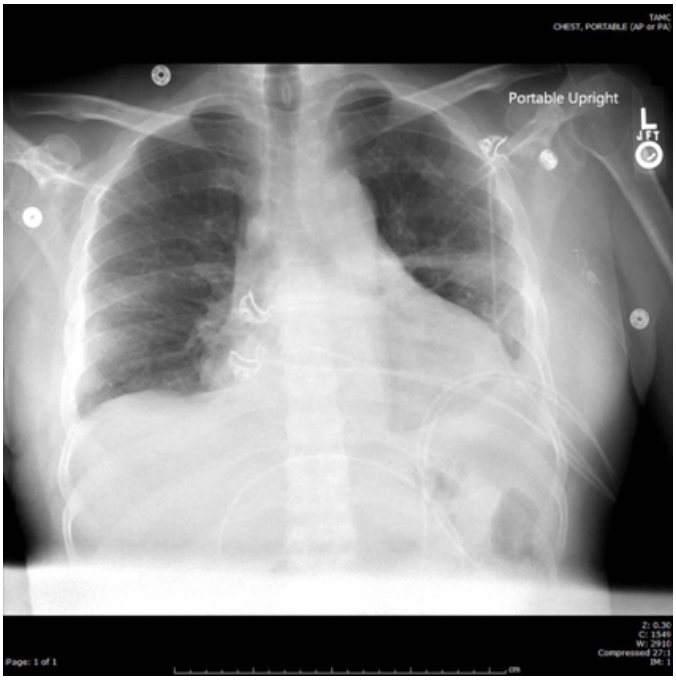


Figure 1: Chest radiograph on admission revealing bilateral pleural effusions and cardiomegaly.

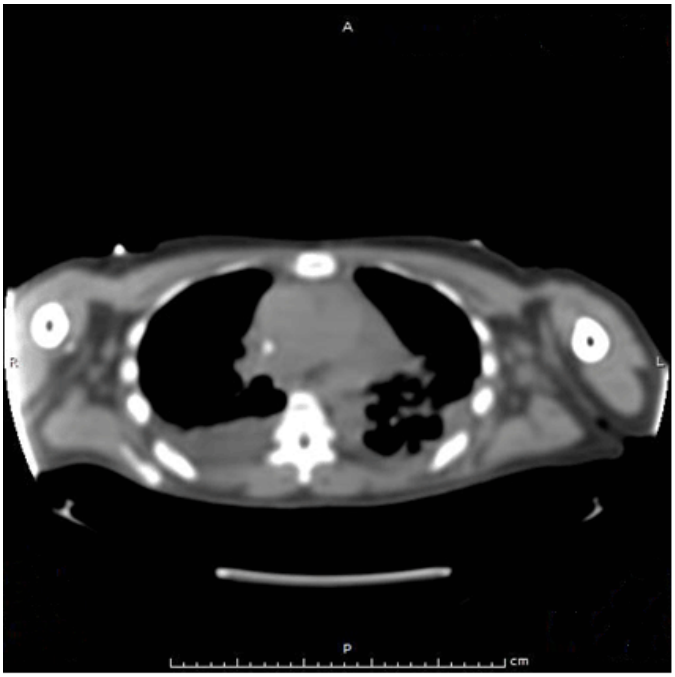

Figure 2: Thoracic computed tomography revealing a pericardial effusion.

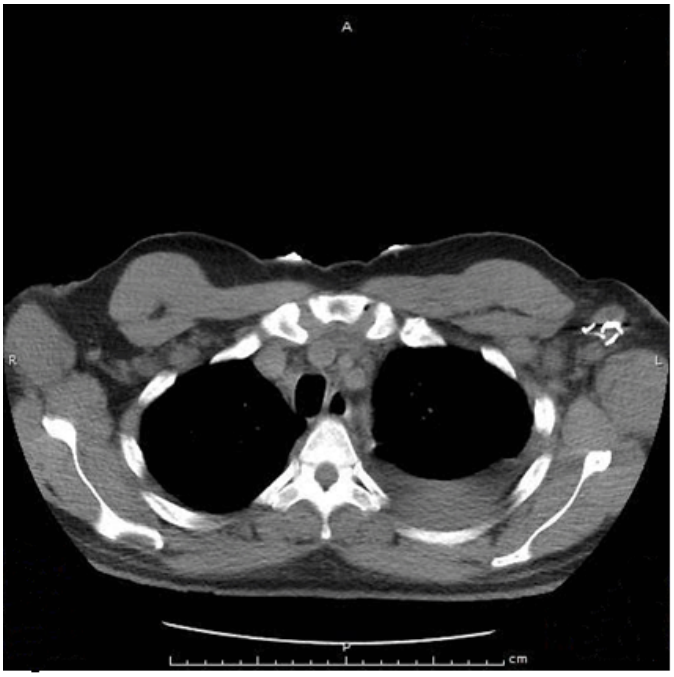

Figure 3: Thoracic computed tomography displaying evidence of surgical clips in the left axilla consistent with a prior lymph node biopsy.

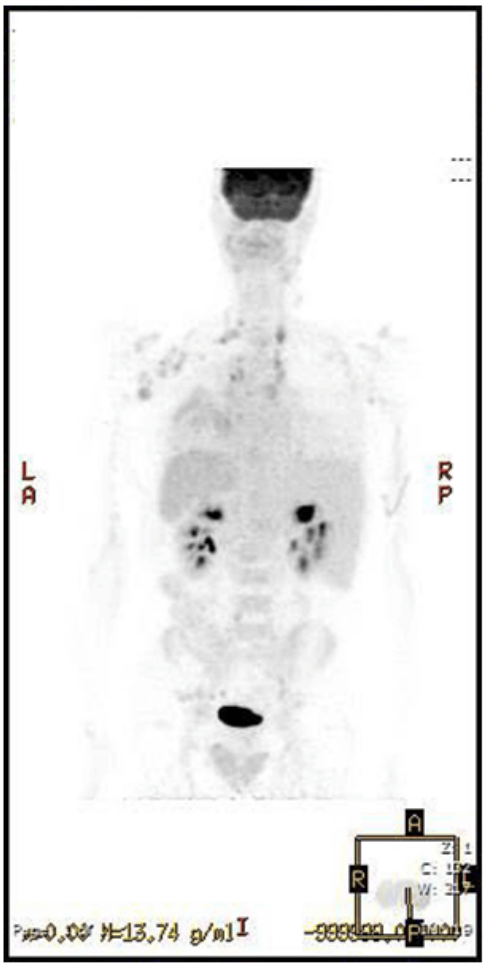


Figure 4: PET-CT scan demonstrating diffuse hypermetabolic lymph nodes in the mediastinum, bilateral axilla, supraclavicular spaces, spleen, iliac, and inguinal regions.

Table 1: Diagnostic criteria for mixed connective tissue disease

| | Serological criteria | Clinical criteria | Diagnosis |
|---|---|---|---|
| Alarcon-Segovia (1987) | Anti-RNP Ab titer > 1:1000 | 1. Edema in hands<br>2. Synovitis<br>3. Myositis<br>4. Raynaud's phenomenon<br>5. Acrosclerosis | Serological criteria plus at least three clinical criteria included either synovitis or myositis |
| | Major criteria | Minor criteria | Diagnosis |
| Sharp (1987) | 1. Myositis<br>2. Pulmonary involvement:<br>a. Diffuse capacity < 70% of normal values<br>b. Pulmonary hypertension<br>c. Proliferative vascular lesions on lung biopsy<br>3. Raynaud's phenomenon or esophageal hypomotility<br>4. Swollen hands<br>5. Anti-ENA Ab > 1:10,000 and anti-U1 RNP Ab positive and anti-Sm negative | 1. Alopecia<br>2. Leukopenia<br>3. Anemia<br>4. Pleuritis<br>5. Pericarditis<br>6. Arthritis<br>7. Trigeminal neuropathy<br>8. Malar rash<br>9. Thrombocytopenia<br>10. Mild myositis<br>11. History of swollen hands | At least 4 major criteria plus anti-U1-RNP Ab titer of at least 1:4000 or two major criteria from among criteria 1, 2 and 3 plus 2 minor criteria plus anti-U1-RNP Ab titer of at least 1:1000<br>Exclusion criteria: positivity for anti-Sm Ab |
| | Common symptoms | Mixed symptoms | Diagnosis |
| Kasukawa (1987) | 1. Raynaud's phenomenon<br>2. Swollen fingers or hands<br>Anti-RNP Ab positive | 1. SLE-like symptoms:<br>a. Polyarthritis<br>b. Lymphadenopathy<br>c. Facial erythema<br>d. Pericarditis or pleuritis<br>e. Leukopenia or thrombocytopenia.<br>2. SSc-like findings:<br>a. Sclerodactyly<br>b. Pulmonary fibrosis, restrictive changes of lung, or reduced diffusion capacity<br>c. Hypomotility or dilatation of esophagus.<br>3. PM-like findings:<br>a. Muscle weakness<br>b. Elevated serum levels of muscle enzymes (CPK)<br>c. Myogenic pattern on EMG | At least one of common symptoms plus positivity for anti-RNP Ab plus one or more signs/symptoms of the mixed symptoms in at least two of the three disease categories |

Table 2: Management based on diseased organ system

| Symptoms/Condition | Treatment Recommendation |
|---|---|
| Fever | Rule out infection/neoplasm |
| Arthralgias, Myalgias | Mild/Non-erosive:<br>Use NSAIDs, antimalarials, and low-dose steroids (prednisone <10 mg/d). Rule out underlying fibromyalgia, depression.<br>Erosive:<br>Use disease-modifying agents such as methotrexate, unless contraindicated; may consider leflunomide or azathioprine. |
| SLE-like rash | Use preventive measures (avoid sun, use of sunscreens), topical steroids, and antimalarials. |
| Raynaud's Phenomena | Keep warm, avoid triggers (caffeine, smoking), protect fingers from injury. Consider use of calcium-channel blockers |
| Pericarditis | Use NSAIDs or steroids (0.25–1.0 mg/kg). Percutaneous and surgical drainage in rare cases of large effusion with tamponade. |
| Renal crisis | Trial of steroids (0.25–1.0 mg/kg) and ACE inhibitor |

Many clinical features are considered typical findings in patients with MCTD to include Raynaud's phenomenon, swollen fingers, erosive arthritis, subcutaneous nodules, along with pulmonary and central nervous system involvement [4]. Cardiac disease has been reported in as high as 65% of patients inflicted with the condition [5]. Our patient was found to have a pericardial effusion, which was likely from pericarditis, which has been reported in up to 43% of MCTD patients [6]. His initial presenting atrial fibrillation was also likely due to his pericarditis [7].

Arthralgia's were likely due to undiagnosed systemic lupus erythematosus and his diffuse pain experienced may be due to a component of fibromyalgia. Given the pathophysiology of his condition, the chronic inflammation was likely the cause of his reactive lymphadenopathy.

There are three different classification assessments that exist: Kasukawa, Alarcón-Segovia, and Sharp, with Alarcon-Segovia considered being simpler than the others (Table 1) [5]. Cappelli et al. performed a retrospective evaluation of 161 patients already diagnosed with MCTD to determine which classification criteria were fulfilled most often [4]. Of the patients, Kasukawa criteria were most sensitive (75%) in comparison to both Alarcon-Segovia (73%) and Sharp (42%) [4]. The additional presence of biomarkers such as anti-U1ribonucleoprotein (RNP) may increase the sensitivity of diagnosis however debate continues to exist regarding this titers specificity [4]. It is likely that future classification schemes will include such biomarkers such as anti-RNP but may also include anti-70kD and HLA-DR4 [8].

No randomized controlled trials have been performed to date regarding optimal treatment for patients with MCTD. In general, they are based on the conventional therapies employed for the individual underlying rheumatic conditions [9]. Medications that have been used include corticosteroids, NSAIDs, hydroxychloroquine, methotrexate, and cyclophosphamide (Table 2). In our patient, we felt that lupus was the predominant condition present; therefore we elected to start a pulse dose of weight-based prednisone (1 mg/kg/day) [10]. Within 24 hours, the patient had improved significantly and he was ultimately discharged on steroids with plans for a slow taper by his outpatient rheumatologist.

Other medications as above can be considered depending on the predominant symptoms: for example primary joint involvement may respond to methotrexate, lower dose corticosteroids may be beneficial for upper gastrointestinal involvement, pericarditis, fever, and oral ulcerations (as would the treatment may be for an SLE flare) [10].

## CONCLUSION

Mixed connective tissue disease (MCTD), is an autoimmune condition affecting almost every major organ of the body, defined by the presence of overlapping features from other connective tissue diseases. The use of available classification criteria and newly available biomarkers can assist in earlier diagnosis. While the condition is considered incurable, prognosis is good with use of glucocorticoid therapy.

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### Author Contributions

Jacob Mathew Jr. – Substantial contributions to conception and design, Acquisition of data, Analysis and interpretation of data, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be published
Tanner Kim – Analysis and interpretation of data, Revising it critically for important intellectual content, Final approval of the version to be published
Timilyn Nunu – Analysis and interpretation of data, Revising it critically for important intellectual content, Final approval of the version to be published
Jay Jahanmir – Analysis and interpretation of data, Revising it critically for important intellectual content, Final approval of the version to be published

### Guarantor

The corresponding author is the guarantor of submission.

### Conflict of Interest

Authors declare no conflict of interest.



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