Section: General Medicine

Case Series

CLINICAL HETEROGENEITY IN MIXED CONNECTIVE TISSUE DISEASE: A CASE SERIES FROM A TERTIARY CARE CENTRE

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ABSTRACT

Background: Mixed connective tissue disease (MCTD) is a rare systemic autoimmune connective tissue disorder characterized by overlapping clinical features of systemic lupus erythematosus (SLE), systemic sclerosis (SSc), polymyositis (PM), and rheumatoid arthritis (RA) in association with high-titer anti-U1 ribonucleoprotein (anti-U1 RNP) antibodies. Owing to its diverse clinical manifestations, diagnosis is often delayed, and management requires individualized treatment based on the predominant organ involvement.

Materials and Methods: We conducted a retrospective observational study of patients diagnosed with MCTD based on Alarcón-Segovia criteria from January 2024 to March 2026 at a tertiary care teaching hospital. Demographic characteristics, clinical manifestations, laboratory parameters, autoantibody profiles, imaging findings, histopathological features, treatment strategies, and clinical outcomes were reviewed and analyzed.

Results: The mean age at presentation was approximately 33 years. Clinical manifestations were markedly heterogeneous with Raynaud's phenomenon and mucocutaneous involvement being the most common presenting features. Severe organ involvement seen in our study included diffuse alveolar hemorrhage; lupus nephritis; autoimmune cytopenias; Sjögren's syndrome; bilateral avascular necrosis of the hip joints; cutaneous lupus. Corticosteroids formed the mainstay of therapy, while plasmapheresis, cyclophosphamide, hydroxychloroquine, methotrexate, and supportive measures were individualised based on the organ involved.

Conclusion: This case series highlights the remarkable clinical heterogeneity of MCTD and emphasizes the importance of early diagnosis, comprehensive multisystem evaluation, and individualized immunosuppressive therapy. Early recognition of anti-U1 RNP-positive overlap syndromes and multidisciplinary management are essential for improving long-term outcomes and reducing irreversible organ damage.

Keywords: Alarcón-Segovia, MCTD, Raynaud’s phenomenon, Overlap syndrome.

INTRODUCTION

Mixed connective tissue disease (MCTD) is a rare systemic autoimmune overlap syndrome characterized by a combination of clinical manifestations of systemic lupus erythematosus (SLE), systemic sclerosis (SSc), polymyositis (PM), and occasionally rheumatoid arthritis (RA),

occurring in association with high-titer anti-U1 ribonucleoprotein (anti-U1 RNP) antibodies. Since its initial description by Sharp and colleagues in 1972, MCTD has remained one of the most intriguing connective tissue diseases because of its evolving phenotype, unpredictable clinical course, and considerable overlap with other autoimmune rheumatic disorders.

The estimated prevalence of MCTD ranges from 2 to 10 cases per 100,000 population, with a marked female predominance of nearly 8:1. The disease commonly presents during the second to fourth decades of life, although pediatric and elderly presentations have also been reported. The etiology remains multifactorial, involving genetic susceptibility, environmental triggers, hormonal influences, and dysregulation of both innate and adaptive immune responses. Human leukocyte antigen (HLA)-DR4 and HLA-DR2 have been implicated in disease susceptibility, while viral infections and environmental factors have been proposed as potential triggers in genetically predisposed individuals.

The hallmark immunological feature of MCTD is the presence of high-titer antibodies directed against U1 ribonucleoprotein (U1-RNP), an essential component of the spliceosome complex involved in RNA processing. Anti-U1 RNP antibodies are highly sensitive for MCTD and form the cornerstone of diagnosis, although they may also be detected in patients with SLE and other connective tissue diseases. These autoantibodies contribute to immune complex formation, complement activation, endothelial injury, and chronic inflammation, resulting in progressive multisystem involvement.

The clinical presentation of MCTD is highly variable and frequently evolves over time. Raynaud's phenomenon is considered the earliest and most common manifestation, occurring in up to 90% of patients. Puffy fingers, inflammatory polyarthritis, myositis, esophageal dysmotility, and mucocutaneous manifestations often follow. Skin involvement includes malar rash, photosensitivity, oral ulcers, alopecia, sclerodactyly, telangiectasia, and lupus-like dermatitis. Musculoskeletal manifestations include inflammatory arthritis, proximal muscle weakness due to inflammatory myopathy, and, less commonly, osteonecrosis resulting from disease activity or prolonged corticosteroid therapy.

Pulmonary involvement represents one of the most significant determinants of long-term morbidity and mortality. Interstitial lung disease and pulmonary arterial hypertension are the most frequently reported pulmonary manifestations and are recognized as major causes of mortality in MCTD. Rare but life-threatening complications such as diffuse alveolar hemorrhage can also be seen. Renal involvement, although less frequent than in isolated SLE, ranges from asymptomatic proteinuria to proliferative lupus nephritis and nephrotic syndrome.

Hematological abnormalities are common and include anemia of chronic disease, autoimmune hemolytic anemia, leukopenia, thrombocytopenia, and pancytopenia. Gastro-intestinal involvement, cardiac and neurological manifestations, though uncommon, may also occur in a subset of patients. Several classification criteria have been proposed for MCTD, including the Sharp, Alarcón-Segovia, Kasukawa, and Kahn criteria. Among these, the Alarcón-Segovia and Kasukawa criteria are most widely used in clinical practice because of their higher sensitivity and specificity. The diagnosis is based on the presence of high-titer anti-U1 RNP antibodies together with characteristic clinical features such as Raynaud's phenomenon, swollen hands, synovitis, myositis, acrosclerosis, or overlap manifestations involving multiple connective tissue diseases.

Management of MCTD is tailored according to disease severity and the predominant organ system involved. Patients with mild disease often respond well to hydroxychloroquine, nonsteroidal anti-inflammatory drugs, and low-dose corticosteroids. Moderate disease involving skin, joints, or muscles may require methotrexate, azathioprine, or mycophenolate mofetil as steroid-sparing agents. Severe organ-threatening manifestations, including diffuse alveolar hemorrhage, pulmonary hypertension, rapidly progressive interstitial lung disease, neuropsychiatric involvement, and lupus nephritis, often necessitate high-dose corticosteroids, cyclophosphamide, rituximab, intravenous immunoglobulin, or plasmapheresis. Advances in immunomodulatory therapy have significantly improved survival, although pulmonary complications remain the leading cause of mortality.

Despite increasing recognition of MCTD, the disease remains underreported, particularly in developing countries, where delayed diagnosis and limited access to specialized investigations often contribute to increased morbidity.

The published literature is a retrospective case series of patients diagnosed with MCTD from January 2024 to March 2026 which comprises isolated case reports of nine patients, reflecting the rarity of this condition. Furthermore, the diverse clinical spectrum and evolving phenotype pose considerable diagnostic and therapeutic challenges.

A total of nine female patients fulfilling the diagnostic criteria for Mixed Connective Tissue Disease (MCTD) with positive anti-U1 ribonucleoprotein (anti-U1 RNP) antibodies were evaluated at our tertiary care centre. Each patient underwent comprehensive clinical assessment, autoimmune evaluation, laboratory investigations, imaging studies, and organ-specific assessment. Management was individualized according to the predominant disease phenotype and severity.

Case 1

A 28-year-old woman with no known medical comorbidities presented to the emergency department with complaints of generalized

weakness for one-month, intermittent fever for ten days, and dry cough for two days.

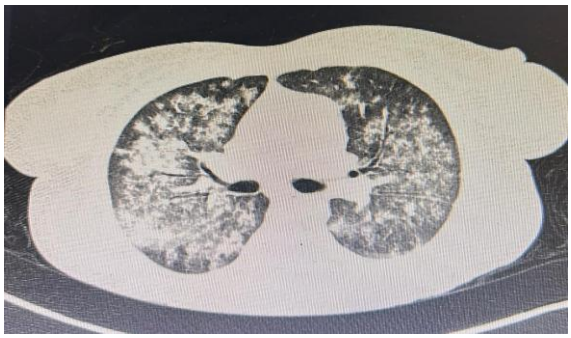
On examination, patient was in significant respiratory distress with a pulse rate of 119 beats per minute and tachypneic with respiratory rate of around 50 breaths per minute. Oxygen saturation was 75% at room air. Pallor was present and Head-toe examination revealed discoloration of the left-hand fingertip. Respiratory system examination revealed bilateral normal vesicular breath sounds with inspiratory crepitations over the (right > left) infrascapular region. Other systemic examination was normal.

Initial laboratory investigations demonstrated pancytopenia with hemoglobin of 7.6 g/dL, total leukocyte count of 2,650 cells/mm³, and platelet count of 100 × 10³/µL; moderate microcytic hypochromic anemia with leukopenia and thrombocytopenia blood picture. Liver function tests revealed mild transaminitis with AST 68 U/L and ALT 38 U/L. Renal function was preserved. Arterial blood gas analysis confirmed type I respiratory failure. Urinalysis showed proteinuria with numerous red blood cells, urine PCR of 1.13. Coagulation profile was normal. Chest radiography demonstrated diffuse bilateral interstitial opacities with haziness involving the mid and lower lung zones. Ultrasound-abdomen showed mild ascites, bilateral pleural effusions, hepatosplenomegaly and preserved renal morphology. Arterial Doppler of the left upper limb showed no significant vascular abnormality.

An extensive infectious disease evaluation was undertaken which was negative. Blood cultures remained sterile. Ferritin levels >1000 ng/mL, while iron studies were normal. In view of the combination of pancytopenia, renal involvement, and respiratory failure, an autoimmune workup was initiated. Complement levels (C3 and C4) were markedly reduced. Antinuclear antibody profile demonstrated strong positivity (3+) for anti-double stranded DNA, anti-SmD1, and anti-U1-snRNP antibodies. Direct Coombs test and Anti-GBM antibody was negative. Anticardiolipin IgG antibodies were weakly positive, IgM antibodies were equivocal, and β2-glycoprotein I IgM antibodies were positive, suggesting possible antiphospholipid antibody syndrome.

HRCT of the chest confirmed diffuse alveolar hemorrhage. Transthoracic echocardiography was normal. The patient was immediately started on steroid pulse therapy, therapeutic plasmapheresis was initiated because of life-threatening diffuse alveolar hemorrhage following which there was marked clinical improvement, permitting successful extubation and transfer from the intensive care unit to the ward. Following stabilization, renal biopsy was done which showed features of lupus nephirits class III/IV for which patient was started on cyclophosphamide induction therapy with other supportive care.

This case highlights an exceptionally severe initial presentation of MCTD with SLE predominance. The coexistence of life-threatening pulmonary hemorrhage, renal disease, hematological abnormalities, and positive lupus-specific autoantibodies necessitated intensive multidisciplinary management and aggressive multimodal immunosuppressive therapy, resulted in reversal of respiratory failure, and stabilization of renal function, underscoring the importance of timely diagnosis and aggressive treatment.



Case 2

A 25-year-old female presented with complaints of progressive facial puffiness for four months, erythematous facial rash for four months, recurrent oral ulcers, fever for one month, with history of use of over-the-counter steroid medications.

On examination, the patient appeared pale with facial puffiness and an erythematous malar rash involving both cheeks. Oral examination revealed extensive whitish plaques over the oral mucosa consistent with active oral candidiasis, associated with leukoplakia and palatal erosions. Multiple erythematous plaques were noted over both cheeks, while diffuse erythematous lesions were also present over the abdominal wall. Systemic examination was unremarkable.

During hospitalization, laboratory investigations confirmed pancytopenia with hemoglobin of 8.6 g/dL, total leukocyte count of 2,270/mm³, platelet count of 82,000/mm³, and an absolute neutrophil count of 1,330/mm³, moderate microcytic hypochromic anemia with leukopenia and thrombocytopenia. Liver function tests showed significant hypoalbuminemia (2.2 g/dL) with otherwise preserved hepatic function. Renal function remained preserved. Urinalysis

demonstrated proteinuria, glucosuria, pyuria and microscopic hematuria, although urine culture showed no bacterial growth. Chest radiograph and ultrasonography of the abdomen revealed bilateral pleural effusions, greater on the right side, with mild ascites, indicating systemic serositis. Inflammatory markers were elevated, Spot urine protein-creatinine ratio was elevated at 1.03. Auto-immune work-up (ANA profile) revealed positivity for U1-snRNP, Anti-Sm, SSA, nucleosome, and histone antibodies, DCT negative, Complement C3 and C4 were low.

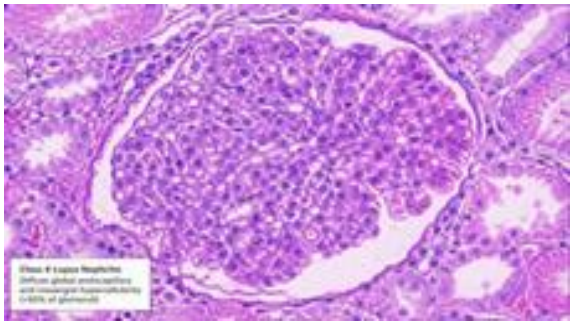
Consequently, pulse corticosteroid therapy was initiated for severe lupus flare. Nephrology consultation was obtained because of persistent proteinuria and low complement levels suggestive of lupus nephritis. Renal biopsy was planned but deferred because of persistent thrombocytopenia, with the recommendation to perform the procedure once the platelet count exceeded 100,000/mm³. Dermatology consultation was also obtained for management of the cutaneous manifestations, and topical corticosteroids, emollients, and strict photoprotection were advised. Simultaneously, oral candidiasis was treated with systemic fluconazole, topical clotrimazole mouth paint, chlorhexidine mouthwash, and supportive oral care following which patient showed significant improvement. She was later discharged on tapering dose of oral prednisolone and steroid sparing agent.

This case represents a severe flare of systemic lupus erythematosus occurring in the setting of mixed connective tissue disease, characterized by prominent mucocutaneous manifestations, pancytopenia with neutropenia, evolving lupus nephritis, serositis, hypoalbuminemia, and concurrent oral candidiasis. Prompt initiation of pulse corticosteroid therapy, broad-spectrum antimicrobial coverage for febrile neutropenia, aggressive antifungal treatment, and multidisciplinary management resulted in significant clinical improvement.

Case 3

A 27-year-old woman, presented to OPD with malar rash, inflammatory polyarthritis, and frothy urine for 6 months. Patient also gave history of Raynaud's phenomenon. On examination, the patient was hemodynamically stable with normal systemic examination. Head-to-toe examination revealed facial puffiness with erythematous malar rash with swelling of small joints of the hand at MCP and PIP, pitting pedal edema

Routine laboratory investigations performed during admission demonstrated mild normocytic normochromic anemia with a hemoglobin level of 10.3 g/dL, while total leukocyte and platelet counts were within normal limits, preserved renal function with a serum creatinine level of 0.9 mg/dL, serum albumin of 2.2, urine routine shows 3+ proteinuria with urine PCR of 11.4 suggestive of nephrotic-range proteinuria. ANA was positive for U1-snRNP, Anti-Sm. Renal biopsy which was done at the time established the diagnosis of diffuse proliferative and membranous lupus nephritis (ISN/RPS Class IV+V). patient was started on six cycles of intravenous cyclophosphamide as induction therapy and had subsequently been maintained on multitarget immunosuppressive therapy consisting of mycophenolate mofetil, tacrolimus, hydroxychloroquine, low-dose prednisolone, weekly methotrexate, and folic acid supplementation. On follow-up, Urinalysis showed a urine protein-creatinine ratio of 0.71, indicating persistent but relatively stable sub-nephrotic proteinuria consistent with maintenance-phase lupus nephritis. As part of routine surveillance for long-term immunosuppressive therapy, ophthalmological evaluation was performed. Examination revealed a central posterior subcapsular cataract, most likely secondary to prolonged corticosteroid therapy. Since visual impairment was not significant and there was no immediate indication for surgical intervention, conservative management with ophthalmology follow-up after six months was advised.



This case illustrates the successful long-term maintenance of a young woman with Class IV+V lupus nephritis. Despite the severity of her initial renal disease, she achieved sustained clinical remission with preserved renal function, stable low-grade proteinuria, and no evidence of active systemic lupus erythematosus. The case also emphasizes the importance of regular multidisciplinary surveillance for treatment-related complications, including corticosteroid-induced cataract, and considering careful tapering corticosteroids to minimize long-term adverse effects without compromising disease control.

Case 4

A 32-year-old female with no previously known comorbidities presented with a two-month history of progressive abdominal pain, abdominal distension, facial puffiness, frothy urine, and bilateral lower limb swelling.

Before presentation to our institution, she had undergone evaluation at a local hospital, where investigations demonstrated severe hypoalbuminemia (serum albumin 1.9 g/dL), moderate ascites on ultrasonography, a left adnexal mass with mildly elevated CA-125 levels (61 U/mL), and progressive anemia. Ascitic fluid analysis revealed a low serum-ascites albumin gradient with lymphocyte-predominant fluid.

However, ascitic fluid adenosine deaminase (ADA) and GeneXpert testing for tuberculosis were negative. CECT of the abdomen demonstrated moderate ascites with omental thickening, suspicious jejunal bowel wall thickening, retroperitoneal lymphadenopathy, and a mildly dilated common bile duct without evidence of choledocholithiasis. Abdominal tuberculosis was initially considered; however, interferon-gamma release assay (IGRA) was negative, making the diagnosis less likely. The patient was subsequently referred to our tertiary care center for further evaluation.

On admission, vitals were stable, general examination revealed significant pallor, bilateral periorbital puffiness, bilateral pitting pedal edema, a small right cervical lymph node, and multiple right supraclavicular lymph nodes. Abdominal examination demonstrated moderate distension with positive shifting dullness, while there was no organomegaly or abdominal tenderness. Cardiovascular, respiratory, and neurological examinations were otherwise unremarkable.

Laboratory investigations done demonstrated hemoglobin level of 9.3 g/dL, normal leukocyte and platelet counts, Renal function remained preserved throughout admission despite marked nephrotic-range proteinuria, with a spot urine PCR of 7.0. Lipid profile revealed hypertriglyceridemia (282 mg/dL), supporting the diagnosis of nephrotic syndrome. Autoimmune evaluation demonstrated strongly positive antinuclear antibodies (3+) with a nuclear fine-speckled pattern. ANA profile revealed strongly positive anti-SmD1 antibodies, along with strongly positive anti-U1-RNP antibodies. Complement levels were markedly depressed, with C3 < 40 mg/dL and C4 < 8 mg/dL.

HPE report of kidney biopsy demonstrated Class IV lupus nephritis which established the diagnosis of systemic lupus erythematosus occurring in association with mixed connective tissue disease. The patient received intravenous pulse corticosteroid therapy followed by oral prednisolone along with initiation of mycophenolate mofetil as induction therapy for Class IV lupus nephritis, along with Ramipril for reduction of proteinuria

Following initiation of immunosuppressive therapy, the patient demonstrated significant clinical improvement and was discharged on oral immunosuppressive agents with advice to follow-up closely with nephrology and gastroenterology, to monitor treatment response, and long-term disease activity.

This case illustrates an unusual initial presentation of MCTD manifesting predominantly as lupus nephritis presenting with extensive serositis-low-SAAG ascites, and severe hypoalbuminemia, closely mimicking abdominal tuberculosis and intra-abdominal malignancy.

Case 5

A 38-year-old woman with no significant prior comorbidities was admitted with 1 week of cough with white expectoration, progressive breathlessness with orthopnea/PND, 1 day of reduced urine output, bilateral leg swelling, and facial puffiness. Initial evaluation revealed microcytic hypochromic anemia with hemoglobin 10.3g/dl, total counts 17793/mm^3, platelets 118000/mm^3, creatinine 1.8mg/dl, urea 30mg/dl with nephrotic-range proteinuria (urine PCR of 47.54), severe hypoalbuminemia of 2.1g/dl, other liver function was preserved. Inflammatory markers were elevated with ESR 84, CRP 3.9. Ultrasonography of the abdomen revealed grad1 renal parenchymal changes with ascites, pleural effusion. Echocardiography showed preserved cardiac function despite markedly elevated NT-proBNP (9170 pg/mL). Autoimmune workup showed low C3 of 74, normal C4 of 17.2 with ANA profile being positive for U1-RNP and SS-A antibodies, immune-mediated glomerulopathy, likely membranous nephropathy. Doppler and CT venography demonstrated extensive right lower limb deep vein thrombosis, along with acute pulmonary embolism and superior vena cava thrombosis, and a small splenic infarct.

She was initiated on IV anticoagulants, pulse intravenous methylprednisolone, hemodialysis in view of oliguria with worsening renal function, following patient improved gradually and was discharged on oral prednisolone with other supportive care, along with consideration for rituximab therapy.

This case highlights the rare and complex presentation of MCTD-associated glomerulopathy with complications requiring dialysis, and widespread venous thromboembolism, underscoring the importance of early recognition, multidisciplinary care, and individualized immunosuppressive therapy.

Case 6

A 46-year-old woman with no known medical comorbidities presented with a one-year history of recurrent painful oral ulcers involving the tongue and oral mucosa, associated with a persistent burning sensation and decreased salivation. She also complained of progressive hair loss and a gradually developing hypopigmented patch over the forehead. The cutaneous lesion was asymptomatic and was not associated with itching, pain, or burning sensation. She also gave history of positive Raynaud's phenomenon.

On physical examination, the patient was conscious, cooperative, and oriented, with stable vital signs. General examination revealed a solitary hypopigmented patch was observed over the forehead, and an ulcer was present on the tongue. Systemic examination, including cardiovascular, respiratory, abdominal, and neurological examinations, was unremarkable. Schirmer's test was performed to evaluate lacrimal gland function and yielded normal results. Routine laboratory investigations were performed which showed anemia of chronic disease, raised inflammatory markers, along with an autoimmune workup of

ANA which was positive (2+), and the ANA profile (ANA-15) demonstrated positivity for anti-SSA/Ro-52 antibodies and anti-Sm/RNP (U1-RNP) antibodies. An otorhinolaryngology consultation was obtained for minor salivary gland (labial) biopsy which further support the diagnosis. Evaluation for other organ involvement were normal.

Dermatology evaluation was sought, diagnosed with secondary alopecia areata, was managed with topical tacrolimus, patient was also started on HCQ, methotrexate, topical measures and other supportive care for dry mouth.

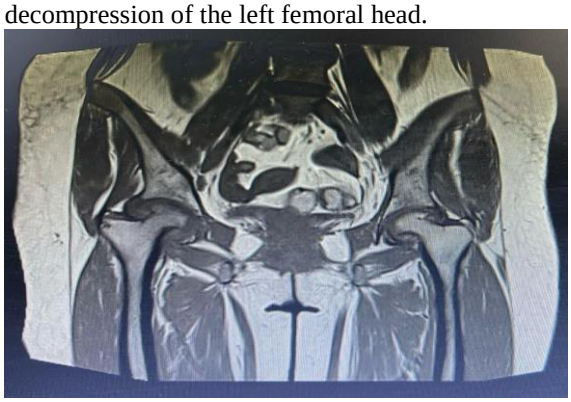
Based on the characteristic serological findings of positive anti-U1-RNP antibodies in conjunction with anti-SSA/Ro-52 positivity and the presence of chronic mucocutaneous manifestations, the patient was diagnosed with mixed connective tissue disease associated with secondary Sjögren syndrome and secondary alopecia areata.

Case 7

A 21-year-old female with no known prior comorbidities presented with a one-year history of progressively worsening low back pain along with both hip pain, accompanied by difficulty in walking, along with a one-month history of intermittent fever and headache.

Her past medical, personal and family histories were unremarkable. On admission, the patient was moderately built and nourished and was hemodynamically stable. General physical examination did revealed pallor. Systemic examination, including cardiovascular, respiratory, abdominal, and neurological evaluation, was essentially normal.

Initial laboratory investigations demonstrated bicytopenia with a hemoglobin concentration of 7.9 g/dL and total leukocyte count of 2.6 × 10^3/µL. In view of the combination of unexplained bicytopenia, intermittent fever, previous history of malar rash, and large joint involvement, an underlying connective tissue disorder was suspected. Autoimmune evaluation revealed a positive antinuclear antibody (ANA) screen (2+), prompting further testing with an ANA profile (ANA-15), which demonstrated positivity for anti-U1 ribonucleoprotein (U1-RNP) antibodies with anti-Sm, establishing the diagnosis of mixed connective tissue disease (MCTD). The bicytopenia was attributed to autoimmune bone marrow suppression secondary to the connective tissue disease. The patient's chronic disabling low back pain prompted further orthopaedic evaluation. MRI of the pelvis performed on 30 January 2026 demonstrated avascular necrosis involving both femoral heads. The absence of traditional risk factors such as corticosteroid exposure, alcohol abuse, or trauma suggested that the osteonecrosis was secondary to the underlying autoimmune connective tissue disorder. Orthopaedic consultation concluded that the patient required surgical intervention, with a plan for right hip core decompression with vascularized fibular grafting along with core decompression of the left femoral head.



Disease-modifying therapy for mixed connective tissue disease was initiated with low-dose weekly methotrexate (7.5 mg once weekly), following which her fever subsided, and her general condition improved significantly.

This case highlights the uncommon presentation of mixed connective tissue disease in a young adult manifesting with autoimmune bicytopenia and bilateral avascular necrosis of the femoral heads at the time of diagnosis, even before exposure to prolonged corticosteroid therapy. The coexistence of hematological involvement and severe osteoarticular complications underscores the diverse manifestations of MCTD and emphasizes the importance of early autoimmune evaluation in young patients presenting with unexplained cytopenias and chronic musculoskeletal symptoms, allowing timely initiation of immunosuppressive therapy and appropriate orthopaedic intervention.

Case 8

A 39-year-old female presented with a three-year history of progressive exertional breathlessness, one-year history of recurrent fever and extensive cutaneous lesions, and a six-month history of oral mucosal lesions. She had been receiving intermittent treatment with methylprednisolone (8 mg) and deflazacort (24 mg) for approximately seven months without a definitive diagnosis or sustained clinical improvement. She also reported episodic Raynaud's phenomenon characterized by bluish discoloration of the fingers on exposure to cold.

On examination, the patient was hemodynamically stable with normal vital parameters. Cutaneous examination demonstrated well-defined hyperpigmented scaly plaques over both malar regions, multiple erythematous plaques involving the upper chest, mid-back, and extensor surfaces of both upper limbs, and numerous hyperpigmented macules and patches over the lower limbs. Diffuse scalp erythema was also noted. Examination of the oral cavity revealed multiple whitish plaques over the buccal mucosa. Cardiovascular, respiratory, abdominal, and neurological examinations were otherwise unremarkable.

Laboratory investigations demonstrated microcytic hypochromic anemia with a hemoglobin level of 7.2 g/dL, while total leukocyte and platelet counts were within normal limits. Liver and renal function tests

were preserved. Inflammatory markers showed a mildly elevated erythrocyte sedimentation rate of 22 mm/hour. Nail-fold capillaroscopy demonstrated dilated tortuous capillaries involving both middle fingers without giant capillaries, hemorrhages, or capillary dropout suggestive of Raynaud's. Autoimmune evaluation showed ANA-IF positive, ANA profile demonstrated strong positivity for anti-U1 ribonucleoprotein (U1-RNP) antibodies. Urine protein-creatinine ratio was 0.25. Two-dimensional echocardiography showed mild tricuspid regurgitation, otherwise normal, six-minute walk test was negative. Skin biopsy was performed, which demonstrated histopathological features consistent with lupus erythematosus and was started on systemic corticosteroid therapy, HCQ along with photoprotection. Although calcium channel blockers were considered for management of Raynaud's phenomenon, nifedipine was deferred because of the patient's relatively low blood pressure.

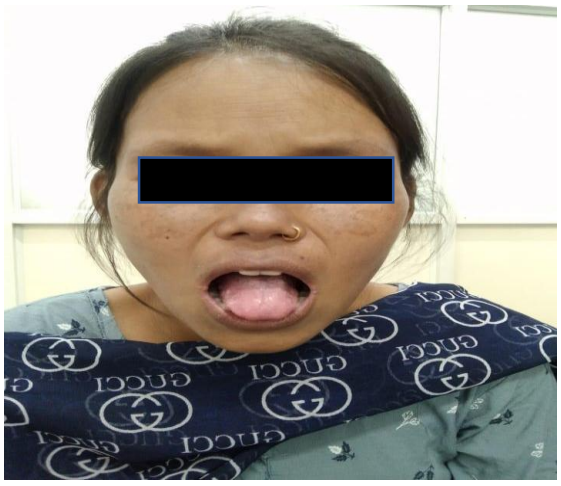
This case illustrates the diagnostic challenges posed by mixed connective tissue disease presenting primarily with chronic mucocutaneous manifestations, Raynaud's phenomenon, constitutional symptoms, and minimal visceral involvement.

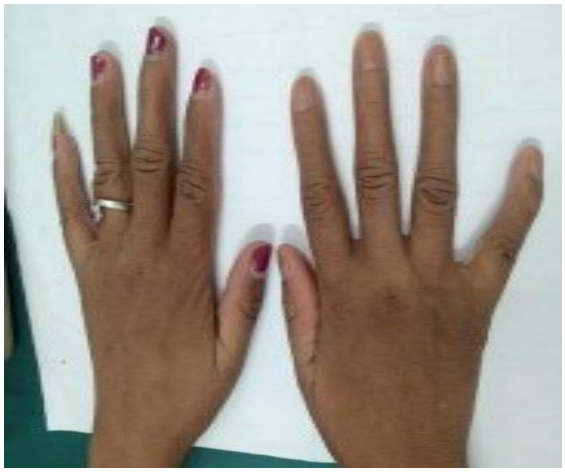
Case 9

A 35-year-old female presented with inflammatory polyarthritis and progressive stiffness of both hands associated pain on exposure to cold for 9 months, complaints of exertional breathlessness for 2 months. Patient was thin built, poorly nourished, stable vitals; clinical examination revealed, diffuse swelling of the fingers with absent creases over DIP joint consistent with puffy hands; Respiratory examination revealed fine basal crepitations with other systemic examination being normal.

Laboratory investigations demonstrated normocytic normochromic anemia with hemoglobin 8.4 g/dL, leukopenia (2,871 cells/µL), normal platelet count and a positive direct Coombs test, suggestive of autoimmune hemolysis. Liver function shows high globulin of 4.5 g/dL, otherwise normal and Renal function remained preserved with serum creatinine of 0.60 mg/dL. Thyroid function tests were within normal limits. Ultrasonography of the abdomen revealed splenomegaly. HRCT thorax showed nodular consolidation with surrounding ground-glass opacification of lungs, mild reticulation mainly in peripheral basal part of bilateral lower lobe, may represent early ILD with NSIP pattern. Two-dimensional echocardiography demonstrated normal chamber dimensions, preserved biventricular systolic function, trivial mitral and tricuspid regurgitation, and no evidence of pulmonary arterial hypertension or pericardial effusion.

ANA by indirect immunofluorescence was strongly positive with a titer of 1:1280 showing a fine speckled pattern with strongly positive anti-U1-RNP (+++), anti-Sm, anti-dsDNA, anti-SSA (Ro), anti-CCP, and anti-Scl-70 antibodies. Additional positivity for nucleosome, histone, ribosomal P protein, and AMA-M2 antibodies was observed. Complement levels were reduced (C3: 0.79 g/L and C4: 0.08 g/L), indicating active immune-complex-mediated disease.





Based on the clinical manifestations and immunological profile, a diagnosis of Mixed Connective Tissue Disease with systemic lupus erythematosus and systemic sclerosis overlap with SSc predominance was established and was started on mycophenolate mofetil and anti-fibrotics like nintedanib.

DISCUSSION

The present case series of nine patients with average age of 33 years at presentation, illustrates the diverse nature of MCTD, ranging from isolated mucocutaneous manifestations to severe life-threatening complications involving the lungs, kidneys, hematological system, and musculoskeletal system.

Clinical Spectrum and Diagnostic Challenges of MCTD

MCTD remains a diagnostic challenge due to its overlapping features with other autoimmune rheumatic diseases. The condition often begins with

nonspecific symptoms such as fatigue, arthralgia, fever, and Raynaud's phenomenon, which may precede the development of more specific organ manifestations over months or years.

In our case series, Raynaud's phenomenon was a common clinical feature observed in five patients, followed by anasarca and skin rashes in four patients. The patients exhibited various dominant phenotypes, majority presenting with SLE-predominant MCTD (seven out of nine), including one SSc-predominant MCTD and one Sjogren's syndrome-predominant MCTD. Among those with SLE-predominant phenotype, four developed with lupus nephritis, one developed avascular necrosis of the hip due to vasculitis, one presented with autoimmune pancytopenia and one with isolated cutaneous lupus.

The wide array of manifestations observed in our cohort highlights the importance of maintaining a high index of suspicion and conducting systematic evaluation of all major organ systems from time to time, even after a patient is categorized under single autoimmune disease. This vigilance is crucial as clinical manifestations change throughout the disease course, evolving from one autoimmune phenotype to another, potentially reflecting the dynamic and complex nature of MCTD.

Limitations

This study has several limitations. The small sample size and retrospective design limit generalization of findings. The follow-up duration was variable, and long-term outcomes could not be assessed uniformly. Nevertheless, the series provides valuable insight into the diverse clinical manifestations and management challenges of MCTD.

CONCLUSION

Mixed connective tissue disease is a complex autoimmune disorder characterized by significant clinical heterogeneity. Early detection of anti-U1 RNP-positive overlap syndrome, along with thorough organ evaluation, and individualized immunosuppressive treatment, is crucial for achieving better outcomes. Long-term, multidisciplinary follow-up is essential to monitor disease progression, prevent complications, and enhance quality of life, given its inherently dynamic nature.

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