Case Study

# A Case of Mixed Connective Tissue Disorder in a Young Female

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We present a case of Mixed connective tissue disorder presented in our institute. Mixed connective tissue disease (MCTD), a rare entity in rheumatology.

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## Introduction

Originally defined in 1972, mixed connective tissue disease (MCTD) is a connective tissue disorder. Its hallmark is high titre of autoantibodies, now called anti-U1 ribonucleoprotein (RNP).[1] It is characterized by overlap syndrome associated selected clinical features of systemic lupus erythematosus (SLE) , polymyositis (PM) and systemic sclerosis scleroderma {SSc}; with anti U1 RNP antibodies.[2]

### *Disease Classification*

According to classification schemes, five major diffuse connective tissue disease {DCTD} exist viz:-- systemic lupus erythematosis {SLE}; systemic sclerosis {scleroderma (SSc)} ; dermatomyositis {DM}; polymyositis and rheumatoid arthritis (RA). Further, a sixth disorder, Sjogren syndrome, is commonly associated with these and but called primary Sjogren syndrome when it occurs alone.[3]

### *Diagnosis and Diagnostic Criteria*

Almost 25% of the patients with systemic symptoms cannot be definitively diagnosed[4]

For diagnosis of MCTD, some characteristic overlapping features of systemic sclerosis (scleroderma SSc), systemic lupus erythematosus (SLE) and inflammatory myopathy; along with high titres of anti-U1 ribonucleoprotein (RNP) are required.

There were several attempts made to standardize the diagnostic criteria of MCTD[5,6]

Sharp, Alarcon-Segovia, Kasukawa, and Kahn are four criteria used to diagnose MCTD but Alarcon-Segovia and Kahn were more favored.[7] The criteria utilized by Alarcon-Segovia had a sensitivity and specificity of 63 and 86 percent, respectively; this accuracy is comparable to that found with the criteria utilized by Kahn (Table 2).

Determination of an overlap syndrome is necessary for diagnosis

There are several hierarchies of antibody response in patients who eventually develop MCTD, with each higher level being associated with an increased expression of the MCTD clinical profile[8,9]

- Level 1 – Positive ANA
- Level 2 – High titer, speckled ANA pattern
- Level 3 – Anti-U1 RNP antibodies
- Level 4 – Anti-68 kD and A' antibodies

U1 RNP consists of ribonucleic acid (RNA) plus three proteins (A', C, and a 68-70 kD protein).

Still basically being an overlap syndrome it must partially or fully diagnose criteria of more than one Rheumatic disorder.

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**Table 1:** Routine workup

| *S.N* | *Investigation* | *Result* | *Normal range* |
|---|---|---|---|
| 1 | TSH | 2.41 mIU/L | 0.465–4.68 |
| 2 | CRP | 649 pg/dl | < 1000 pg/dl |
| 3 | RA FACTOR | Non- reactive | Cut-off <10/UL |
| 4 | ANTI-CCP IgG | 5.02 AU/mL / NEGATIVE | Cut-off >30U/mL |
| 5 | CK | 269.7 U/L | 30-135 U/L |
| 6 | LFT Globulin Titre | 4.6 g/dl | 2-3.5 g/dl |
| 7 | LFT A/G ratio | 0.9 | 0.8-2.0 |
| 8 | TLC | 8320* 10^3/ µL | 4000–11000*10^3/ µL |
| 9 | Urine Routine | Within normal limits | Within normal limits |
| 10 | RFT | Within normal limits | Within normal limits |
| 11 | Upper GI endoscopy | Normal study | Normal study |
| 12 | Chest Xray | Within normal limits | Within normal limits |
| 13 | 2 D Echo | Normal study | Normal study |

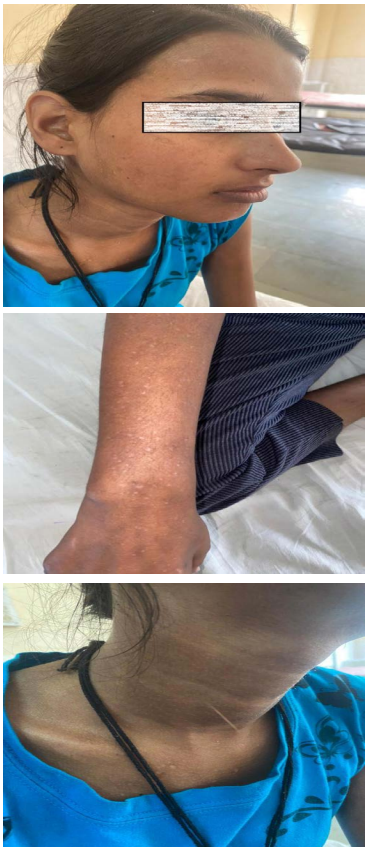

**Figure 1:** Dermatological lesions, on face malar rash and on forearm hypo-hyperpigmented area

## *Case Report*

A 18 year old female, presented to OPD with complaints of Joint pains in multiple joints of body since 4 years, myalgia since 4 years, cold insensitivity with painful blue and swollen fingers on cold water etc exposure since 4 years and a reddish patch over face and multiple whitish speculated skin lesions over the exposed areas of body since 2 years. Recently she developed fever, intermittent, responding to antipyretics OTC since 2 months, she also developed abdominal epigastric burning sensation with relation to food intake and generalized body weakness.

While she was taking OTC and symptomatic treatment all these years she was never properly evaluated for these complaints. Medical records were non-existent and she had no significant past history other than those associated with these symptoms.

On examination, her vitals were GC- Fair, BP- 100/60 mmhg , P- 92/min regular, Afebrile on examination , Micro-Ostia noted with she able to put her 2 fingers only on wide open mouth, with oral ulcers. Macular skin lesions noted over face and exposed area of neck but sparing nasolabial folds, she also complained of hair fall, but no scarring over scalp was appreciated. Also there was hyperpigmentation and depigmented areas with whitish looking patches over exposed area of bilateral upper and lower limbs. (Figure 1)

There were no localised signs of inflammation over joints, no signs of arthritis but joint movements in small joints of fingers and both shoulders were painful. She apparently could not comb her hairs by herself due to proximal muscle weakness. There was clinically appreciable muscle weakness in bilateral shoulder joints abduction and on circumduction movements; hence, power was graded as 4/5 over shoulder joints bilaterally. There was mild epigastric tenderness. There was visible puffiness and swallowing of fingers.

Other systemic examination was unremarkable.

## *Laboratory Investigations and Workup*

Preliminary laboratory investigations were unremarkable except for Lymphocytic predominance noted in TLC

**Table 2:** Immunological workup

| *Investigation* | *Estimated Titre* | *Interpretation a/c lab cut-offs* | *Remarks* |
|---|---|---|---|
| ANA By IFA | 1:1000 | Strong Positive | SPECKLED PATTERN Cut-off > 0 Positive |
| ds DNA ANTIBODY NcX | 211.26 IU/mL | Positive | Cut-off > 100 Positive |
| U1-snRNP (68KDa) IgG | 1284 EliA U/mL | Positive | Cut-off > 2910 Positive |
| Jo-1 Antibody IgG | 2.23 RU/mL | Negative | Cut-off < 20 Negative |
| Centromere Antibody IgG | 1.18 RU/mL | Negative | Cut-off < 20 Negative |
| Sm Antibody IgG | 85.50 RU/mL | Positive | Cut-off > 20 Positive |
| RNP- Sm Antigen IgG | 200 RU/mL | Positive | Cut-off > 20 Positive |
| Scl 70 IgG | 0.46 RU/mL | Negative | Cut-off < 20 Negative |
| SSA-RO (Soluble substance A) IgG | 9.40 RU/mL | Negative | Cut-off < 20 Negative |
| SSB- La(Soluble substance B) IgG | 1.14 RU/mL | Negative | Cut-off < 20 Negative |

with total counts 5220/uL(Table 1). Peripheral smear was unremarkable. RA factor and Anti-CCP antibodies were non-reactive/negative and ANA by IFA was positive with estimated titre 1:1000. (Table 2). Xray of Hand & wrist was unremarkable and evidence of any joint destruction or synovitis was seen. USG w/a was normal except for few subcentrimetric sized mesenteric lymph nodes noted.

Preliminary laboratory investigations were unremarkable except for Lymphocytic predominance noted in TLC with total counts of 5220/uL and 45% lymphocytes and ALC of 2349/uL. Peripheral smear was unremarkable. RA factor and Anti-CCP antibodies were non-reactive and ANA by ELISA was positive with absolute value 7.61u/l (Cut-off > 1.2U/L). Xray of Hand and wrist was unremarkable and evidence of any joint destruction or synovitis was seen. USG w/a was normal except for few subcentrimetric sized mesenteric lymph nodes noted.

After ruling out any acute infectious agent for her complaints of intermittent fever, arthralgia, and abdominal pain we suspected for rheumatological processes.

## Discussion

Rheumatoid arthritis was ruled out due to absence of any evidence of joint erosion or other sequel, normal radiological studies of joints, along with a negative RA and Anti CCP IgG titre.

On immunological studies antibodies, titres of patient satisfied entry criteria of SLICC and ACR for SLE, but it was not fulfilled adequately due to lack of sufficient clinical criteria. Patient has high titre of ANA antibody of speckled pattern > 1:1000 and high titre of anti Sm IgG 85 RU/ml, but lack of sufficient clinical criterias for SLE diagnosis.

There was prominent complaint of the Raynauds phenomenon and dyspepsia along with MicroOstia of mouth opening commonly associated with systemic sclerosis, but those criteria were also not fulfilled. For SSc patient neither has sufficient clinical criteria's nor immunological criteria, Scl70 antibodies were negative.

**Table 3:** Two algorithms for establishing a diagnosis of mixed connective tissue disease (MCTD)

| *Alarcon-Segovia's criteria* | *Kahn's criteria* |
|---|---|
| A. Serological criteria | A. Serological criteria |
| Anti-RNP antibodies with a hemagglutination titer of ≥1:1600 | High titer anti-RNP corresponding to a speckled ANA of ≥1:1200 titer |
| B. Clinical criteria | B. Clinical criteria |
| 1. Swollen hands | 1. Swollen fingers |
| 2. Synovitis | 2. Synovitis |
| 3. Myositis* | 3. Myositis |
| 4. Raynaud's phenomenon | 4. Raynaud phenomenon |
| 5. Acrosclerosis | |
| MCTD is present if: | MCTD is present if: |
| Criterion A is accompanied by three or more clinical criteria - one of which must include synovitis or myositis. | Criterion A is accompanied by Raynaud phenomenon and two or more of the three remaining clinical criteria. |

Dermatological lesions of malar rash sparing nasolabial folds over exposed head and neck areas were present, as seen with SLE . Along with it multiple whitish speculated skin lesions over the exposed areas of body pointed towards SScd-like picture like "salt and pepper" appearance.

POEMS syndrome was excluded with absence of diabetes and normal thyroid profile and absence of myxoedema (POEMS-Polyneuropathy, Organomegaly, Endocrinopathy, Monoclonal gammopathy, and Skin changes).

There was no renal involvement with renal profile, and urine examination was within normal ranges,. All these pointed to a mixed or undifferentiated picture
Patient had a high ANA titer by IFA 1:1000 with speckled pattern with high U1-snRNP 1284 EliAu/ml (Serum, Fluoroenzymeimmunoassay), along with evidence of myositis with raised CK, prominent complaints of Raynauds phenomenon, and complaints of puffy swollen fingers.

A further distinction between SLE and MCTD has been made recently in an analysis of the immunoglobulin classes associated with the anti-U1 snRNP response. In SLE patients, anti-U1 snRNP commonly belonged to both the IgG and IgM classes, whereas IgG antibodies in the absence of IgM were typical of MCTD patients **[10].** This was observed in our patient.

In our patient there was evidence of myositis by clinically appreciable proximal muscle weakness which was not a presenting complaint. CK was raised as observed in other studies in similar subsets of U1-RNP positive cases within similar range values. In a study aimed at determining the clinical phenotype of a patient with positive Anti u1RNP antibodies, Maria Casal-Dominguez *et al*., observs that

*"At the onset of disease, muscle weakness was less prevalent among anti-U1-RNP-positive patients (15%), patients with anti-U1-RNP autoantibodies had higher median CK 229. [11]"*

Patient was fulfilling *Alarcon-Segovia's criteria and Khans critera* (Table 3) and hence was diagnosed as a case of mixed connective tissue disorder (MCTD) {Table 3}

### *Disease evolution of MCTD*

In a large population based prospective cohort study, Reiseter, S., Gunnarsson et al observes that *"Among 118 patients, 14 (12%) developed another well-defined rheumatic condition other than MCTD after mean disease duration of 17 (SD 9) years. There were 13% of patients in remission throughout the mean observation period of 7 (SD 2) years."* [12]

Hence the diagnosis of MCTD is unlikely to change in a 5 year follow up period but evolution and remission can be seen in longer follow-ups.

Original Table from *Bennett RM. Overlap Syndromes. Kelley's Textbook of Rheumatology, 8th Edition, W.B. Saunders Co, Philadelphia 2009*

### *Treatment*

The original description of patients with mixed connective tissue disease (MCTD) emphasized the relatively good prognosis and excellent response to glucocorticoids [13] As noted above, these patients have a low prevalence of serious renal disease and life-threatening neurologic problems [14].

Mixed connective-tissue disease (MCTD) can range from milder diseases that can be treated in an outpatient basis to severe forms. Milder forms are treated primarily as an outpatient as most disease is mild in these patients. Nonsteroidal anti-inflammatory drugs (NSAIDs), antimalarials (e.g., hydroxychloroquine), and corticosteroids are the mainstay of therapy. Immunosuppressive drugs are generally reserved for treating specific clinical manifestations and when there is major organ involvement.

Fortunately, in our patient disease was milder, our patient was started on NSAIDS initially, hydroxychloroquine and oral steroids. She had no signs of PAH. She showed clinical improvement within a fortnight with resolution of complaints. She was discharge on similar treatment with advice to regular follow-up. Further follow-up and evaluation is planned for the patient to study the disease natural history and evolution.

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