

MIXED CONNECTIVE TISSUE DISEASE: THE KING FAISAL SPECIALIST HOSPITAL EXPERIENCE

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Background: The aim of this study was to assess the clinical presentation, complications and serological analysis of mixed connective tissue disease (MCTD) at King Faisal Specialist Hospital & Research Centre (KFSH&RC), and to determine the long-term clinical and immunologic outcomes.

Patients and Methods: This was a retrospective study with prospective follow-up of 18 patients with MCTD who were followed at KFSH&RC between 1982 and 1999.

Results: The age at onset of the disease ranged from 6 to 44 years, with a mean age of 17.9 years. The female to male ratio was 2.5:1, and the mean follow-up time was 5 years. The most frequent presenting symptoms were arthralgia in all patients, Raynaud's phenomenon in 16 patients (88%) and swollen hands in 11 patients (61%). Arthritis was seen in 12 patients (67%) and definite myositis in 10 patients (58%). The most common skin rashes encountered included lupus-like rash in 8 patients (44%), scleroderma-like rash in 8 patients (44%), and cutaneous vasculitis in 5 patients (28%). Pulmonary hypertension occurred in 4 patients (22%). Other clinical manifestations encountered were esophageal hypomotility in 10 patients (56%), myocarditis in 2 patients (11%) and proteinuria in 2 patients (11%), while various neurological manifestations were present in 7 patients (39%). All patients exhibited high titer of ANA and anti-nRNP antibodies. Five of the 18 patients (28%) had marked reduction in the anti-nRNP during remission. Following treatment, features of inflammation as well as Raynaud's phenomenon and esophageal hypomotility diminished, while pulmonary hypertension persisted. A favorable outcome was observed in 12 patients (67%); 3 patients (17%) had continued active disease, while 3 patients (17%) died, with death related to pulmonary hypertension occurring in two patients (11%).

Conclusion: The studied patients demonstrated the typical clinical and serological findings of MCTD, which support the correlation between anti-nRNP antibody specificities and MCTD. Autoantibody reactivity against nRNP polypeptides tends to regress during prolonged disease remission. The majority of our patients had favorable outcomes, with pulmonary hypertension being the most frequent disease-associated cause of morbidity and mortality.

Ann Saudi Med 2002;21(1-2):43-46.

Key Words: Mixed connective tissue disease, arthralgia, Raynaud's phenomenon, myositis.

Mixed connective tissue disease (MCTD) was first described by Sharp and co-workers in 1972¹ as an apparently distinct rheumatic disease whose clinical characteristics included a combination of features similar to those of systemic lupus erythematosus (SLE), scleroderma and polymyositis, in the presence of high titers of circulating antibody to nuclear ribonucleoprotein (nRNP). Several attempts have been made in recent years to standardize the diagnostic criteria for MCTD.^{2,3} Alarcon-Segovia and Cardiel³ tested 593 patients with connective tissue disease for three proposed criteria for MCTD.

Patients and Methods

Eighteen patients followed up in the Rheumatology clinics at King Faisal Specialist Hospital and Research Centre (KFSH&RC) between 1982 and 1999 were selected for this study based on the classification criteria of Alarcon-Segovia and Cardiel (Table 1).

The laboratory evaluations included Westergren erythrocyte sedimentation rate (ESR), hemoglobin levels (Hb), white blood cell (WBC) count, platelet count, urinalysis, serum creatinine, creatine phosphokinase (CPK), lactic dehydrogenase (LDH), ANA, antibodies to double-stranded DNA (ds DNA), RNP, anti-Smith (Sm), SSA and SSB, anticardiolipin (aCLs) and rheumatoid factor (RF). Patient sera were sampled two to three times a year or more often when clinically indicated.

Anemia was defined as Hb level <100 g/L, leukopenia as a WBC <3.5x10⁹/L, and thrombocytopenia as a platelet count of <140x10⁹/L. Muscle biopsy and electromyogram

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Accepted for publication 28 February 2002. Received 27 May 2001.

TABLE 1. *Alarcon-Segovia diagnostic criteria.*

Serological criteria
Positive anti-nRNP at a hemagglutination titre of 1:1600 or higher
Clinical criteria
Edema of hands
Synovitis
Myositis (laboratory or biopsy proven)
Raynaud's phenomenon (2 or 3 color phase)
Acrosclerosis (with or without proximal scleroderma)

For definite diagnosis, serological criteria plus at least three out of the five clinical criteria are required.

(EMG) were performed when indicated by the presence of clinical symptoms and elevated muscle enzymes. Impaired pulmonary function was defined as reduced CO diffusion capacity (<75%), restrictive pattern or signs of pulmonary fibrosis on high-resolution CT scan. Pulmonary hypertension was evaluated by *M*-mode echocardiography. Hypomotility of the esophagus was examined by barium meal x-ray. Antinuclear antibodies (ANA) were detected by immunofluorescence.

Enzyme-linked immunosorbent assay (ELISA) has been used at our institution since 1990 for the detection of anti-DNA, anti-nRNP, anti-Sm, anti-SSA and anti-SSB antibodies, and also for RF. Hemagglutination test was used from 1982 to 1990 to detect the RNP. The presence and severity of disease activity were determined by abnormalities demonstrated during periodic systemic evaluation. Patients were considered to be in remission when there was no evidence of disease activity or only mild Raynaud's phenomenon, normal function of major organs and normal overall functional activity level for more than one year, with prednisone >5 mg/day. Patients were considered as having continuing active disease when there was major organ involvement that required cytotoxic drug therapy and/or prednisone >15 mg daily.

Results

Demographic Features

The 18 MCTD patients were followed up over a period of 1-17 years, with a mean follow-up time of 5 years. Female to male ratio was 2.5:1. The onset of the disease development among the patients ranged from 6 to 44 years, with a mean age of 17.9 years. In most patients, the disease evolved over time, and all patients ultimately met the MCTD classification criteria of Alarcon-Segovia's.^{2,3} (Table 1).

Clinical Characteristics

The clinical characteristics of the 18 MCTD patients are as shown in Table 2. Raynaud's phenomenon was the presenting symptoms in 16 patients (89%), while 10 of the patients (56%) presented with swollen hands. Other skin abnormalities encountered were lupus-like skin changes (malar rash and photosensitivity) in 8 patients (44%), scleroderma-like skin changes in 8 patients (44%), and cutaneous vasculitis in five patients (28%). All the patients

complained of polyarthralgia, either at presentation or during their follow-up. Arthritis was present in 12 patients (67%), and of those, five had rheumatoid-like arthritis with positive RF, but none of them had destructive arthropathy. Hand x-ray showed soft tissue calcification in one patient.

Ten of the 18 patients (56%) had definite myositis and of those, one presented with characteristic rash of dermatomyositis. Esophageal dysfunction secondary to lower esophageal hypomotility was detected in 10 patients (56%). Pulmonary manifestations were present in nine patients (50%), four of whom had pulmonary hypertension. Restrictive pulmonary function test was detected in five patients, three of whom were found to have lung fibrosis by high-resolution CT scan of the lung, and four with pleural effusion.

Cardiac manifestations were myocarditis in two patients, of whom one had severe heart failure which was successfully managed with steroid and antifailure therapy. Pericarditis was detected in three patients.

Three recurrent aseptic meningitis was reported in one patient during her nine-year follow-up, with complete recovery on steroid treatment. Other neurological manifestations encountered were carpal tunnel syndrome in two patients, seizure disorder in two patients, and peripheral neuropathy in one patient.

Two patients in our series developed nephrotic range proteinuria, and kidney biopsy showed membranous glomerulonephritis in one patient who also tested positive for anti-d-DNA. The second patient had no kidney biopsy done as she died before full investigation.

Associated autoimmune disease was found in three patients, two with autoimmune hepatitis and one with autoimmune thyroiditis.

Laboratory Results

The laboratory results of the patients are as shown in Table 3. Leukopenia was detected in four patients. No evidence of thrombocytopenia was noted in our series. All patients had highly positive ANA in speckled pattern. Anti-nRNP were positive in all our patients, most of them with high titer (>2000 by ELISA and >1:1600 by hemagglutination method). Reduction in anti-nRNP titer was observed in five patients who achieved remission (Table 4). In 10 patients with persistently high anti-nRNP, seven were in remission while three were in continued active disease.

Low titer of anti-dsDNA antibodies were present in three patients who presented with lupus-type skin rash. Three patients had positive IgG aCLs, and of these, one had severe pulmonary hypertension, but no features of antiphospholipid syndrome were detected.

Treatment and Outcome

No standard treatment protocols were followed in this study. The treatment used included low (<10 mg - >10-30 mg/day), moderate and high-dose corticosteroids (>30

TABLE 2. Clinical features of the 18 MCTD patients.

Age	Sex	Raynaud's	Swollen hand	Arthritis/Arthralgia	Myositis	Skin	DLCO	Pulm HTN	Serositis	Esophagus
6	F	+	+	A	-	SCL vasculitis	?	-	-	-
9	F	+	+	A	-	SCL vasculitis	?	-	+PL, Pe	-
10	F	-	-	A	+	-	N	+	-	-
10	F	-	-	A	+	-	?	-	+Pe	-
15	F	+	+	A	+	Vasculitis	-	-	+PL	-
16	F	+	+	a	+	SLE	-	-	-	+
18	F	+	-	A	+	SCL/SLE	N	-	-	+
21	M	+	-	A	+	SLE	?	-	+PL	+
22	F	+	+	A	-	SCL vasculitis	-	+	-	+
26	M	+	-	a	-	SLE	N	-	+PL	-
30	M	+	+	a	+	SCL vasculitis	N	-	-	+
31	F	+	+	a	+	SLE/SCL	N	-	-	+
34	M	+	+	a	+	SLE dermatomyositis	-	-	-	+
37	F	+	-	A	-	SLE	-	+	+Pe	-
38	F	+	+	A	+	SCL	-	-	-	+
41	F	+	+	a	-	-	?	-	-	+
40	F	+	-	A	-	-	?	+	-	-
44	F	+	-	A	-	SCL/SLE	-	-	-	+

A=arthritis; a=arthralgia; SLE=lupus-like skin change; SCL=scleroderma-like skin changes; PL=pleural effusion; Pe=pericardial effusion.

TABLE 3. Laboratory findings.

Laboratory data	No. of patients
Anemia (Hb<10)	2
Leukopenia (WBC<3.5)	4
Thrombocytopenia (Plt<140)	0
ANA (speckled)>1:1280	18
RNP (high)	18
Low complement (CH50<300, C3<0.05)	1
Anticardiolipin Ab (IgG)>15	3
Anti-dDNA(+ve)	3
Anti Sm	0
Anti SSA/SSB	1
Anti Scl 70	1
RF+ve	10

TABLE 4. Baseline and follow-up anti-nRNP antibody titer.

Patient	RNP (at presentation)	RNP (at most recent presentation)
1	1:1887	>2000
2	1:1928	>2000
3	>2000	>2000
4	1:6400	1:6400
5	818	199
6	1:3200	>2000
7	>2000	>2000
8	1:1876	>2000
9	>2000	74
10	>2000	500
11	1:81,200	165
12	>2000	>2000
13	>1:40,000	53
14	>2000	>2000
15	>2000	>2000
16	>2000	>2000
17	>2000	>2000
18	>2000	>2000

mg/day) in combination with disease-modifying agents (methotrexate, hydroxychloroquine, D-penicillamine, and azathioprin).

Twelve patients achieved complete remission while three had continued reactive disease. Of those, two had pulmonary hypertension with severe Raynaud's phenomenon and one had membranous glomerulonephritis. Three patients died.

Discussion

This retrospective study summarizes the clinical and serological features of 18 patients with MCTD, followed up at KFSH&RC from 1982 to 1999. Previous studies have shown that MCTD evolves over time,^{4,6} and the information obtained in this present study confirmed this view. In an initial report of MCTD over a short-term follow-up, the disease tended to be responsive to corticosteroid therapy and to have a relatively favorable prognosis.¹ Subsequent studies^{6,10-12} emphasized that pulmonary hypertension was the major, sometimes fatal, complication in MCTD. Our study confirmed these observations, in which pulmonary hypertension was estimated to be present in 24% of our patients.

The leading cause of death among in this series was pulmonary hypertension, and this was a contributing factor in two of the three patients who died. IgG aCLs was detected in three of our patients, one of them with severe pulmonary hypertension, which is consistent with other reports of the association of these antibodies with pulmonary hypertension in MCTD and SLE.^{6,13,14} The other two patients had only low titer of IgG aCLs without recurrent thrombosis or abortion, which was consistent with previous observation.^{15,16}

The long follow-up in our study provided us an opportunity to determine the evolution of anti-nRNP antibody responses in MCTD. Only five of the 12 patients with prolonged remission showed substantial reduction of anti-nRNP titer. This was contrary to the observation by Burdt et al.,⁶ who found marked reduction of RNP titer in most of their patients whose MCTD was in prolonged remission. This discrepancy, however, could be due to the relatively small number of our patients compared to that of Burdt et al.⁶

Renal involvement occurs in MCTD with relatively poor prognosis.⁶⁻⁹ Nephrotic syndrome associated with membranous nephropathy is the most common presentation, and may respond to high-dose corticosteroid therapy.⁷ In our study, two patients had renal involvement, one of them with nephrotic syndrome associated with membranous nephropathy with persistent proteinuria, despite a high dose of steroid and azathioprine. The second patient had nephrotic range proteinuria, but no kidney biopsy was performed as the patient died of pneumothorax.

Neuropsychiatric problems in our MCTD patients were found to have a 33% incidence. Recurrent aseptic meningitis was found in one patient who showed rapid response to corticosteroid therapy. Harris et al. described a young lady with recurrent aseptic meningitis as a presentation of MCTD.¹⁷ Also Bennett et al.¹⁸ reported four patients with episodes of aseptic meningitis in their review of neuropsychiatric problems of 20 MCTD, and this makes aseptic meningitis one of the distinct feature of MCTD neurological manifestation.

In this study, our 18 patients demonstrated the typical clinical and serological findings of MCTD, which support the correlation between anti-nRNP antibody specificities and MCTD. Autoantibody reactivity against nRNP polypeptides tends to regress during disease remission. The majority of our patients had favorable outcomes, with pulmonary hypertension being the most frequent disease-associated cause of morbidity and mortality.

Acknowledgements

The authors would like to thank Miss Evelyn Dinio and Miss Alma Bautista for typing this manuscript.

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