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Mixed Connective Tissue Disease and Systemic Lupus Erythematosus in One Family†

Michael R. Lubetsky, MD* and Howard Duncan, MD*

A mother with mixed connective tissue disease (MCTD) and a daughter with systemic lupus erythematosus (SLE) were simultaneously diagnosed and treated in August, 1977. Multiple cases of SLE occurring in the same family are not rare, but the frequency with which systemic lupus erythematosus and mixed connective tissue disease occurs in the same family is not known, and the reports are few. This report describes these two cases and suggests that mixed connective tissue disease may be part of the spectrum of systemic lupus erythematosus.

In 1972 Sharp, *et al* defined the entity "mixed connective tissue disease"[1] (MCTD) in patients who had some features of systemic lupus erythematosus, of scleroderma, and of polymyositis. They postulated that it may represent a distinct rheumatic disease syndrome which is invariably associated with a specific extractable nuclear antigen (ENA) in the serum.

In August, 1977, a mother and daughter were seen in different clinics at Henry Ford Hospital where they presented with almost identical clinical pictures consistent with a connective tissue disorder. They were hospitalized within several weeks of each other. An interesting feature of this mother-daughter combination is that the mother was felt to have mixed connective tissue disease with a positive test for antibodies to ENA-RNP antigen and the daughter to have systemic lupus erythematosus (SLE) with a positive test for antibodies to Sm antigen.

Case Reports

Case 1

The mother, a 45-year-old black woman, was seen at Henry Ford Hospital on June 1, 1977 complaining of burning in her chest, which occurred mostly in a supine position. At the first office visit, she described a bitter taste in her mouth but had no complaints referable to her joints. There was no history of Raynaud's phenomenon, muscle weakness, or dysphagia.

The past medical history revealed that she had been treated with gold for rheumatoid arthritis in 1974. She also had been hospitalized elsewhere from December, 1976 through February, 1977, and a diagnosis of collagen disease had been suggested. Her major symptom at that time was chest pain. While treatment with corticosteroids had improved her condition, it became worse when the drug was discontinued about three weeks before her first Henry Ford Hospital visit.

Her physical examination was within normal limits except for tenderness over her ribs and sternum. There was no evidence of synovitis and no residue of the so-called rheumatoid arthritis.

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*Department of Internal Medicine, Division of Rheumatology, Henry Ford Hospital

Address reprint requests to Dr. Lubetsky, Henry Ford Hospital, 2799 W Grand Blvd, Detroit, MI 48202

She returned on July 21, 1977 because her right wrist had become painful and swollen two days earlier. Examination revealed synovitis in her right wrist, swelling and tenderness of the metacarpal phalangeal joints, and weakness of the proximal musculature of the upper and lower limbs. There was also some skin tightness and swelling of her fingers. At that time, there were scattered, dry rales at the lung bases and over the right middle lobe with tenderness over the right lower ribs. During her hospitalization, she related a recent history of Raynaud's phenomenon, dry mouth, dry eyes, and she developed parotid gland swelling.

Laboratory studies (see table) included a hemoglobin of 9.5 mg %; Westergren sedimentation rate of 68 and 109 mm/hr; CPK 811 I.U./L; LDH 735 I.U./L; SGOT 86 I.U./L; Aldolase 35 u/L; gamma globulin 3.17 gm/dl; IgG greater than 3,000 m/dl; VDRL reactive, FTA nonreactive; antinuclear factor strongly positive, strong threads and weak to medium homogeneous leukocyte specific, titer less than 640;[2] C-4 15 mg/dl (18-53); C-3 and CH 50 normal; twenty-four hour urine for protein 0.134 gm per volume; creatinine clearance 120 ml/min; positive antibodies to ENA with RNP antigen titer greater than 1 to 2,048; negative anti-DNA antibodies. Chest x-ray showed several dense strands of infiltrate or atelectasis at the left base and a left pleural effusion; sialogram of the left parotid gland showed some saccular dilatation of the proximal part of the main parotid gland. An electromyogram was consistent with a myopathy. Pulmonary function tests showed restrictive changes with decreased diffusing capacity. Muscle biopsy of the left quadriceps was reported as "interstitial myositis with vasculitis." Endoscopy showed esophagitis, superficial gastritis, and hiatal hernia. Esophageal manometry showed an incompetent lower esophageal sphincter.

It was felt that the patient's clinical and laboratory picture was consistent with the diagnosis of mixed connective tissue disease, and she was treated with prednisone 40 mg daily. Her esophageal reflux was treated symptomatically.

Since her discharge on September 2, 1977, she has been followed in the outpatient department and up to June, 1978 had done well, despite an episode of herpes zoster at C-3, C-4 dermatomes. She also continues to have costochondritis and some esophageal reflux. The extractable nuclear antigen, RNP antigen, remains the same.

Case 2

The daughter, a 30-year-old black woman, was in good health until April, 1977, when arthralgia began to occur, mainly affecting the hands and feet. She also noted dysphagia, nausea and vomiting, fever at night, cough and progressive weakness. She was hospitalized elsewhere on two different occasions in May and June without any specific diagnosis being given. She also related a history of weight loss. Her medications consisted of aspirin and iron pills. On her first visit to Henry Ford Hospital on August 3, 1977, a physical examination revealed slight skin tightness of her hands, feet and face, tender metacarpal and metatarsal phalangeal joints and wrists with swelling and warmth of the latter, proximal muscle weakness of her arms and legs, and diffuse tenderness of the chest wall. A history consistent with Raynaud's phenomenon was also obtained. Laboratory results (see table) included a hemoglobin of 9.7 mg %; Westergren sedimentation rate of 96 mm/hr; gamma globulin 3.24 gm/dl; IgG greater than 2400 mg/dl; CPK 981

COMPARATIVE LABORATORY DATA

	Antinuclear Factor	Extractable Nuclear Antigen	Anti-DNA Antibodies	Complement	Muscle Enzymes	Immuno-globulin	Chest X-ray	Muscle Biopsy	Pulmonary Function Tests	Manometry
Case 1: Mother	Strongly Positive Strong Threads and Weak to Medium Homogeneous Leukocyte Specific < 640	Positive RNASE Sensitive RNP Antigen > 1:2048	Negative	C4 15 mg/dl (18-53) C3 and CH50 Normal	↑ CPK and Aldolase	↑ ↑ IgG	Infiltrates at bases Left pleural effusion	Interstitial Myositis with Vasculitis	↓ Diffusing Capacity Predicted 21.7 Actual 7.97 39% of Predicted	Incompetent Lower Esophageal Sphincter
Case 2: Daughter	Strongly Positive Strong Threads and Weak to Medium Homogeneous Leukocyte Specific < 640	Positive Sm Antigen	Positive Anti-IgG IgM	C4 8 mg/dl (18-53) C3 and CH50 Normal	↑ CPK and Aldolase	↑ ↑ IgG	Negative	Interstitial Myositis with Vasculitis	↓ Diffusing Capacity Predicted 25 Actual 11.95 49% of Predicted	Incompetent Lower Esophageal Sphincter

I.U./L; aldolase 23 u/L; SGOT 58 I.U./L; C-4 8 mg/dl (18-53); C-3 and CH 50 normal; twenty-four hour urine for protein 0.530 gm per vol; and creatinine clearance 72 ml/min. Antinuclear factor was reported as positive, strong threads, medium to strong homogeneous, leukocyte specific titer less than 640;[2] ENA was positive for antibodies to Sm antigen and positive anti-DNA antibodies both IgG and IgM. Chest x-ray was negative. Electromyogram of the biceps and deltoid suggested a myopathic process. Muscle biopsy of the left deltoid was reported as "interstitial myositis with vasculitis," and pulmonary function tests showed diffusing capacity to be decreased. Esophageal manometry revealed an incompetent lower esophageal sphincter, and esophagoscopy showed esophagitis and hiatal hernia. The diagnosis of systemic lupus erythematosus with some sclerodermatous features was made, and she was started on prednisone 40 mg daily.

The patient has improved symptomatically and as of June, 1978 was receiving prednisone 10 mg daily. She also experienced an episode of herpes zoster at the C-8 dermatome in April, 1978 and was hospitalized in May, 1978 for possible central nervous system involvement because of a change in her mental status. The antibodies to extractable nuclear antigen have remained unchanged, i.e., positive to Sm antigen.

Discussion

Instances of systemic lupus erythematosus occurring in the same family have been reported[3-5] but, according to Sharp,[6] information is not available on the frequency with which SLE and mixed connective tissue disease (MCTD) occur in the same family. Dr. Evelyn Hess has identified two MCTD patients in Cincinnati whose families have other connective tissue diseases.[6] In one family one person has SLE and RA, and in the other, two family members have lupus. There also has been a recent report of two siblings in Michigan with mixed connective tissue disease.[7] Five other members of the family discussed in this paper were screened for a connective tissue disease. While the antinuclear factor was negative in all, it is worth noting that C-4 levels were low in three, since C-4 levels were also low in the cases reported here.

The two patients described in this paper presented with very similar findings, and yet their serologic studies classified one as MCTD and the other as SLE. Although the daughter is believed to have systemic lupus erythematosus because of positive antibodies to Sm antigen and positive anti-DNA antibodies, her case could be diagnosed on a clinical basis as MCTD because it fulfills Sharp's characteristics of polyarthritis or polyarthralgia, Raynaud's phenomenon, diminished esophageal motility, decreased pulmonary diffusing capacity, swollen hands and myositis.[8] These circumstances narrow the distinction between MCTD and SLE and support the concept the MCTD is not a separate entity but consists of a subset within the spectrum of SLE.[9,10] Other supporting evidence includes the fact that about half of the 25 MCTD cases in Sharp's original series had at least four of the American Rheumatism Association's preliminary criteria for systemic lupus erythematosus.[11] This was also true for the mother with MCTD in this report, who had Raynaud's phenomenon, arthritis, chronic false positive serologic test for syphilis, pleural effusion, and hemolytic anemia. Another point linking MCTD and SLE is the occurrence of antibodies against a nuclear RNP antigen in about 40 to 50% of all SLE patients.[10] If MCTD falls within the spectrum of SLE, it would be a milder form since renal disease is uncommon in mixed connective tissue disease while kidney involvement is a primary cause of death in systemic lupus erythematosus. Moreover, in the follow-up study on the first MCTD patients after 8 to 25 years, seven patients have died, but probably only two died from manifestations of MCTD.[6] This finding also suggests that MCTD is a more benign form of connective tissue disorder.

It is possibly not important to decide if mixed connective tissue disease is indeed a separate entity but rather to emphasize the fact that patients with an overlap syndrome who have positive antibodies to ENA-RNP antigen usually respond well to steriods and have a more favorable prognosis.[8]

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