Mixed connective tissue disease is a distinct overlapping syndrome with features of rheumatoid arthritis, systemic lupus erythematosus, polymyositis and scleroderma along with U1-RNP antibodies, which can progress to lupus or scleroderma.

**Defining Mixed Connective Tissue Disease**

Mixed connective tissue disease (MCTD) is a connective tissue disorder first described in 1972 as a distinct rheumatic disease syndrome associated with a specific antibody to an extractable nuclear antigen (ENA). This early report was based on a group of patients with overlapping clinical features of systemic lupus erythematosus (SLE), scleroderma, and myositis with blood tests showing a distinct autoantibody. This autoantibody was later identified as an antibody to U1-ribonucleoprotein (RNP).

**Features**

Features of MCTD include arthritis/arthritis, acrosclerosis, esophageal dysmotility, polymyositis, sclerodactyly, (scleroderma-like tissue hardening), pulmonary hypertension or interstitial lung disease, and high levels of anti-U1RNP antibodies as well as antibodies against U1-70kd small nuclear ribonucleoprotein (snRNP), which are known as U1-RNP antibodies.

**Who is Affected?**

Females are 10 times more likely to develop mixed connective tissue disease than males. The typical onset occurs in people aged 15-25 years. In the United States, MCTD is seen in about 3-5 out of 100,000 persons, and it’s more prevalent than dermatomyositis and less prevalent than SLE. Internationally, MCTD has a reported prevalence of 2.7 cases per 100,000 population.

**Symptoms and Signs**

At the time of diagnosis 74 percent of patients show signs of Raynaud phenomenon and 66 percent of patients exhibit symptoms of arthralgia and arthritis. Over time, nearly all patients show signs of Raynaud phenomenon and arthritis, and eventually about 66 percent of patients develop esophageal hypomotility, swollen hands, and pulmonary (respiratory) dysfunction.

Other signs and symptoms seen in MCTD include myositis (muscle inflammation), leukopenia (low white blood cell count), sclerodactyly, pleuritis/pericarditis (inflammation of tissue surrounding the lungs and heart), and rash. Complications include fever, which occurs as a sign of infection, vasculitis, pancreatitis, appendicitis, bowel perforations, trigeminal neuralgia, respiratory distress syndrome, stroke, and secondary Sjogren’s syndrome.

Although some researchers recognize MCTD as a subset or early stage of SLE, most researchers consider MCTD a distinct clinical entity with infrequent renal complications. While the prognosis in MCTD is generally good, patients who develop pulmonary hypertension are more likely to have an unfavorable disease course. Overall, about 25 percent of patients with MCTD eventually progress to SLE, and about 33 percent progress to systemic sclerosis. Pulmonary hypertension is the most common cause of death in MCTD, followed by scleroderma renal crisis, heart failure and infections.
Diagnosis
MCTD is diagnosed in patients with symptoms of arthritis, scleroderma, and Raynaud with high titers of anti-nuclear antibodies with a speckled pattern and high titers of anti-RNP and anti-U1-70kd antibodies. Patients may also have rheumatoid factor, Scl-70 antibodies, and antiphospholipid antibodies. Current diagnostic criteria include 3 of the 5 following clinical features: edema of hands, swollen joints (synovitis), myositis, Raynaud phenomenon and acrosclerosis (sausage-like fingers typically seen in systemic sclerosis).

Treatment
The type of treatment used depends on the predominant signs and symptoms, the organs that are affected, and the clinical disease severity. Nonsteroidal anti-inflammatory drugs (NSAIDs) are used to reduce pain and inflammation, which improves mobility and function. Hydroxychlorquine (Plaquenil) is frequently used along with NSAIDs in patients with arthritis. Patients with more severe disease are often treated with low-dose corticosteroids, endothelin receptor antagonists, cyclophosphamide, or methotrexate or with cyclooxygenase-2 inhibitors. Patients with secondary pulmonary hypertension are usually treated with prostaglandins such as eposprostenol (Flolan). Patients who show a good response to corticosteroid or NSAID treatment usually have a favorable prognosis.

Resources
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