CLINICAL VIGNETTE

Mixed Connective Tissue Disease – The Grey Area

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The patient is a 51-year-old female seen for an initial visit. Her chief concern was overwhelming fatigue and, indeed, she was previously diagnosed in 2003 with Chronic Fatigue Syndrome. In addition, she reported positive "autoimmune" tests including antinuclear antibody and rheumatoid factor tests, and she was told she had Rheumatoid Arthritis. Her chief manifestation for this was bilateral metacarpophalangeal joint pain. She had never been on any disease modifying agents. She also noted diffuse myalgias and felt her fingers were often cold and turned red easily, which was consistent with Raynaud's phenomenon.

Her past medical history was significant for celiac disease managed with a combination of a gluten and dairy free diet, which improved her diarrhea, right hip trochanteric bursitis, vasovagal syncope, and migraine headaches. Her only medications were Valtrex 500 mg a day and Advil as needed.

On physical examination, she appeared fatigued. Her temperature was normal at 98 degrees; her other vital signs were stable. Her exam was notable for a normal cardiac exam with no murmurs and clear lung fields. An office spirometry was also normal. Her abdominal exam was nontender with no organomegaly. Her skin exam revealed no rash. Her fingers were pink and puffy with no evidence of synovitis at any of her joints. Her neurological exam revealed subtle weakness with hand grip on the left. An electromyogram and nerve conduction study was normal.

Her blood work revealed mild leukopenia with lymphopenia but was otherwise normal. She had a negative urine sediment. Her antinuclear antibody test was positive at 1:320 and her rheumatoid factor was positive. However, her anti-double stranded DNA antibody test, nDNA (Crithidia) antibody test, and SSA/SSB antibodies were all negative. She had a mild positive IgM Cardiolipin Ab test. Rheumatology was consulted and the diagnosis of a mixed connective tissue disease was suggested. An RNP antibody test was ordered and was strongly positive at 113 (strong positive is > 80U). Her Sm antibody was negative.

Discussion

This case highlights the difficulty in diagnosing non-specific symptoms with positive autoimmune tests. The patient has carried a diagnosis of both Chronic Fatigue Syndrome and Rheumatoid Arthritis. While difficult to do at times, the importance of arriving at an accurate diagnosis lies in its therapeutic and prognostic implications.

Mixed connective tissue disease or MCTDx is characterized by overlapping symptoms or features of at least two systemic autoimmune diseases.[1] These diseases include Systemic Lupus Erythematosus (SLE), Systemic Sclerosis (SSc), Polymyositis/Dermatomyositis (PM/DM), and Rheumatoid Arthritis (RA).

As in our patient, the serologic marker of MCTDx is the presence of antibodies to the U1 small nuclear ribonucleoprotein autoantigen or U1 sn RNP. It was first described in 1972 by Sharp et al[2] and their patients had a favorable prognosis. There is a 10:1 female predominance with an age of onset usually in the second or third decades.

Recent larger studies have helped to better define the epidemiology, clinical features, and prognosis of MCTDx. In 2011, Gunnarson et al[3] conducted a nationwide retrospective study in Norway and found 147 adult Caucasian patients with the diagnosis of MCTDx for a point prevalence of 3.8/100,000. The largest recent study in 2013 by Hajas et al[4] found that polyarthritis, Raynaud's phenomenon, puffy fingers, and sclerodactyly were the most prevalent symptoms at the time of diagnosis. A review of the literature from 2003/2013 revealed that polyarthritis, Raynaud's phenomenon, puffy fingers, interstitial lung disease, and esophageal dysmotility are the most frequently reported symptoms when following patients with MCTDx.[1] In addition, fatigue and myositis are common. However, cardiovascular events secondary to accelerated atherosclerosis and thrombosis, as well as progressive pulmonary fibrosis and pulmonary artery hypertension (PAH),[4] are the most serious complications of MCTDx.[5-9] Of note, the most frequent cardiac manifestation of MCTDx is a pericardial effusion.

In addition to the clinical findings, several hematologic and serologic abnormalities are common including anemia, leukopenia (particularly lymphopenia), hypergammaglobulinemia, rheumatoid factor, and anticyclic citrullinated peptide (CCP) antibody. While these are common, they are not universal. The one serologic finding in all patients with MCTDx is a positive ANA with specificity to the anti-U1 ribonucleoprotein (RNP),[10] which is one of the specific antibodies to extractable nuclear antigen (ENA).

The treatment of mixed connective tissue disease is often unsatisfactory for mild to moderate symptoms as glucocorticoids are reserved for clinical manifestations of the disease with significant morbidity including aseptic meningitis, myositis, pleurisy, pericarditis, and myocarditis. Fortunately, there is a low prevalence of serious neurological and renal disease. Unfortunately, pulmonary hypertension, which is the main cause of death in these patients, is often refractory to glucocorticoid therapy. Routine echocardiography is recommended for all patients with the diagnosis of MCTDx to detect early pulmonary hypertension.[11] Other treatment options include anti-malarial agents and immunosuppressive medications.

Clinical Pearls/Board Review Key Points

1) Common symptoms for MCTDx include the following: fatigue, polyarthritis, Raynaud's phenomenon, puffy fingers, and sclerodactyly.
2) The serologic marker for MCTDx is the presence of high titers of anti-U1 RNP antibody (also called anti-ENA antibody).
3) Routine screening for patients with MCTDx includes annual echocardiography for early detection of one of the most serious complications – pulmonary hypertension. However, the most common cardiac manifestation is a pericardial effusion.

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