INTERESTING CASE OF MIXED CONNECTIVE TISSUE DISORDER

JENNIFER MATHEW KOVOOR
Department of General Medicine,
THANJAVUR MEDICAL COLLEGE

Abstract:
Mixed connective tissue disease (MCTD) has features common to lupus, scleroderma and myositis with high levels of antibodies to U1 ribonucleoprotein (U1 RNP). Its prevalence among patients with rheumatism has been reported to be low in India by Malaviya et al. (0.3) and Nedumaran et al. (0.125)20,26. Here we are presenting a 35 yr old lady with one month history of joint pain, dysphagia, exertional breathlessness and dry gangrene of upper limb. On evaluation she was found to have features of scleroderma (sclerodactyly, esophageal dysmotility), Rheumatoid arthritis (small joint pain and stiffness), Raynauds phenomenon, Interstitial lung disease with pulmonary hypertension, minimal renal involvement and no neurological involvement, with high titres of serum anti U1RNP levels, arterial Doppler showing intimal atherosclerotic plaque. We are reporting this case due to the unusual presentation of MCTD as Pulmonary hypertension even at the onset of symptoms, which indicates the multivariate effect of anti U1RNP in the disease process.

Keyword: MCTD, anti U1RNP, Interstitial lung disease, Esophageal dysmotility, Raynauds phenomenon, Sclerodactyly

INTRODUCTION
In 1972 Sharp and his colleagues first described the interesting association of SLE, Scleroderma, Polymyositis with an antibody called Anti U1RNP. Serologic features showed high titre of ANA (1:10,000), anti U1RNP, anti Smith, anti Ro, La antibody positivity. U1RNP is responsible for hand edema, arthritis, raynaud’s phenomenon, inflammatory muscle disease, sclerodactyly. The SLE criteria was first proposed by Hochberg 1997. Accordingly Classic SLE is the one which satisfied many criteria, Definite SLE had 4 or more criteria, Probable SLE had 3 criteria, Possible SLE had 2 criteria. Latent/incipient lupus was described by Schur 1993 who belongs to either probable or possible SLE class. Surprisingly still there were leftouts known as Undifferentiated connective tissue disorder (UCTD) an entity who had some but not all features of RA, SLE, Sjogrens. 75% of them never fulfilled any criteria-mosca 2004. But it was von Muhlen CA who first found...
out the association of a specific antibody (antiU1RNP) among a subset of UCTD which were later subclassified as MCTD. The association of following antibodies with SLE, known as Antids DNA (40-90%), anti Sm (15-30%), anti-rRNP (10-20%), anti PCNA (3%) were known since 1996. Presence of Ro ab alters the clinical picture in the form of severe systemic symptoms, interstitial pneumonitis, vasculitis, congenital heart block and subacute skin manifestations. U1RNP is a uridine rich RNA complexed with 7 proteins 70 kDa (tan 1989) found in 30-40% of active SLE (terborg (1990)). But Hof in 2005 found that anti U1-70K subunit of nRNP appearing as apoptotic bleb, is more superior marker of early MCTD.

CASE REPORT

35yr old Mrs Vimala, homemaker presented with history of painful blackish discolouration of left middle finger, small joint pain of upper limb, dysphagia for one month and acute onset chest pain and dyspnoea, with history of two spontaneous abortions. On examination patient has features of microstomia, sclerodactyly, skin thickening of face and hands, oral candidiasis. No calf muscle tenderness, suggestive of DVT, upper limb pulses weak bilaterally with dry gangrene of left middle finger distal phalanx. Vitals showed sinus tachycardia, 130/min, RR of 30/min, SpO2 of 90%, normal BP. System examination showed loud palpable second heart sound pulmonary component, bilateral basal velcro crepitations, with no neurological involvement, no muscle weakness, no organomegaly per abdomen. Investigations showed albuminuria 4+, normal complete hemogram, elevated erythrocyte sedimentation rate, normal renal and liver function tests, chest x-ray showed prominent pulmonary artery trunk, ECG showed right bundle branch block, P pulmonale, right axis deviation. Ultrasound abdomen and pelvis showed normal sized kidneys. 24 hour urine protein showed 408 mg/1700ml/day. Pulmonary function tests showed restrictive pattern. HRCT chest plain showed bilateral reticulonodular pattern of lower lung lobes, no wedge shaped infarct, no hilar lymphadenopathy. Vascular Doppler of both upper limbs showed atherosclerotic plaque occluding left brachial artery proximal part 50% and distal part to 90%. Aorta, subclavian, renal artery, lower limb arterial and venous Doppler normal. Echo showed main pulmonary artery, right atria and ventricle dilated, mild pulmonary hypertension, TRPG 35 mmHg, grade 2 tricuspid regurgitation, No RWMA, IAS, IVC intact, normal LV ejection fraction. Coagulation profile showed elevated D dimer 1388. Immunological profile showed strong positivity for Antinuclear antibody, anti Smith antibody, anti Ro, Anti U1 RNP antibody, Rheumatoid factor antibody, elevated Creatine kinase, Anti ds DNA antibody, anti Scl - 70, anticardiolipin antibody, antiphospholipid antibody were negative. CT pulmonary angiography was not done as the facility was not available at our hospital. Patient was started on Inj cyclophosphamide, pulse dose, oral steroids, sildenafil, hemorrhheological agents, dihydropyridine calcium channel blockers, antiplatelets and statins.
Mixed connective tissue disease (MCTD) was described more than 30 years ago and has clinical features common to systemic lupus erythematosus (SLE), progressive systemic sclerosis (PSS) and inflammatory myositis.[1] It has a female : male prevalence of 16:1. And has the onset in the 2nd to 3rd decade of life. Acquired causes of U1RNP antibody are due to exposure to vinyl chloride, silica,
or ingestion of procainamide. There is an antibody response to the spliceosome complex, involved in the processing of pre messenger RNA. An antibody against the uridine-rich U1 ribonucleoprotein (U1 RNP) characterizes the disease. This antibody reacts with two components of the small nuclear ribonucleoprotein (snRNP), U1 RNA and 70 K polypeptide. This antigen is the ribonuclease sensitive fraction of the extractable nuclear antigens (ENA), which was identified initially by enzyme denaturation and haemagglutination. Most studies use the Kasukawa et al criteria as they do not exclude patients with Sm positivity, and quantitative values for U1 RNP are not needed. The prevalence of MCTD depends on the criteria used. In Smolen and Steiner’s cohort (Alarcon-Segovia criteria) only 70 % satisfied the Sharp criteria.

Kasukawa et al Diagnostic criteria

Common symptoms

Raynaud’s Phenomenon
Swollen fingers or hands Presence of Anti U1 RNP Mixed findings
A. SLE like
Polyarthritides Pericarditis / pleuritis
Lymphadenopathy Facial erythema
Leucopena/thrombocytopenia

B. Scleroderma like Sclerodactyly Pulmonary fibrosis Esophageal dysmotility

C. Polymyositis like Muscle weakness High CPK Myopathic EMG

Requirement for diagnosis: At least one common symptom, with positive U1 RNP antibodies and one or more findings in at least two of the three categories A, B and C.

Clinical features

Myositis, serositis, lymphadenopathy, aseptic meningitis. Musculoskeletal involvement are in the form of joint pain, stiffness, tenosynovitis, deformities. Features of Raynaud’s phenomenon, swollen digits, malar rash, discoid plaques, sicca complex may confuse the diagnosis at times when it occurs in isolation. Exertional dyspnoea, tachycardia, bibasilar crackles and features of right ventricular failure are suggestive of pulmonary hypertension. Unlike scleroderma where there is interstitial fibrosis, the mechanism here is intimal proliferation and medialized hypertrophy of pulmonary arterioles. Renal involvement is rare (25%) because high titres of anti U1 RNP is protective against diffuse proliferative glomerulonephritis, if at all any involvement it would be membranous glomerulonephritis, renovascular hypertensive crisis of scleroderma kidney. GIT involvement in the form of dysmotility, portal hypertension, splenic vascularitis, megacolon, protein losing enteropathy, autoimmune hepatitis, primary biliary cirrhosis, pancreaticitis, diverticulitis. CNS involvement in the forms of trigeminal neuralgia, psychosis, convulsions, aseptic meningitis, cerebral hemorrhage, transverse myelitis, PMLE, optic atrophy, peripheral neuropathy, retinal vasculitis. High titre of anti U1 RNP is protective against serious renal and neurological complications compared to SLE. Hematological manifestations include anemia, thrombocytopenia, leukopenia, hypocomplimentemia.

Complications

Pulmonary hypertension (PHT), usually a late-stage complication, is the most common cause of death in mixed connective tissue disease (MCTD), occurring in up to 38% of patients. It has got a rapid accelerated course compared to any other connective tissue disorder. However,
controversies on the very existence of such an entity have come up.[8-10]

**Investigations**

Antibodies to U1 RNP have been identified in other connective tissue diseases.[11] The concept of a good prognosis in MCTD has also not stood the test of time.[12] Upregulation of intercellular adhesion molecule-1, endothelial leukocyte adhesion molecule-1 and Class II MHC molecules on pulmonary artery endothelial cells as well as the endothelial cell-binding activity of U1 RNP antibodies are considered to mediate PAH.[17,18] Anti-endothelial cell antibodies also have been reported to be higher in patients with active disease.[19] Chest xray shows pulmonary involvement in the form of interstitial infiltrates, pleural thickening. CT chest shows honey combing,septal thickening predominantly lower zone. ECHO with Doppler ultrasound is the commonest screening tool and should be performed to establish a baseline at initial diagnosis of MCTD.[22] Echocardiography may show right ventricular enlargement and pulmonary hypertension.

Pulmonary function testing (PFT) including diffusing capacity of the lung for carbon monoxide (DLCO) is a necessary part of the evaluation of all patients, primarily to exclude or characterize the contribution of underlying airway or parenchymal lung disease. A fall in DLCO in a patient with scleroderma/MCTD and normal lung volumes is suggestive of the development of pulmonary arterial hypertension. PFTs with DLCO should be performed periodically (every 6-12 months) to improve detection of pulmonary vascular or interstitial disease with ECHO every 1-2 years, especially if the patient has had symptoms of connective tissue disease for more than 10 years. Formal assessment of exercise testing, typically 6-min walk test helps determine disease severity, response to therapy and progression.

**Treatment**

Once the diagnosis of PHT has been established, general approaches to treatment include supplemental oxygen for hypoxemia to maintain oxygen saturations >90% at all times, continuous positive airway pressure therapy and treatment of other contributing factors such as chronic thromboembolic disease with warfarin, right ventricular failure with diuretics and digitalis etc. Patients who respond to vasodilator testing have an improved long-term survival with the use of calcium channel blockers.[23] Prostacyclin derivatives (epoprostanol (IV), treprostinil (subcutaneous), iloprost (inhaled), beraprost (oral)) are potent vasodilators with antiplatelet aggregatory effects that have been shown to primarily improve exercise tolerance and survival to a lesser extent. Endothelin antagonists (bosentan, sitaxsentan, ambrisentan) block endothelin-1, which is a potent vasoconstrictor and smooth-muscle mitogen that might contribute to the increase in vascular tone and the pulmonary vascular hypertrophy associated with PAH.[24] Other agents that are currently being evaluated include phosphodiesterase inhibitors such as dipyridamole and sildenafil, inhaled nitrous oxide and arginine supplementation.[25] Surgical techniques including lung transplant remain the mainstay of treatment for patients with PHT who are unresponsive to medical management.

**REASON FOR THE CHOOSING THE CASE**

This case was selected due to its rarity and presentation as terminal events like pulmonary hypertension (due to Interstitial lung disease, arteriopathy) / corpulmonale.
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