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Case study
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Mixed Connective Tissue Disease: The Dilemma of Diagnosis

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Abstract

Having a case with typical clinical features and specific serological markers can help the practitioner to reach a definitive diagnosis, and accordingly, provide proper management plan. However, it may not always be the case when confronting systemic diseases, particularly Autoimmune Connective Tissue Diseases (AICTD). Conditions characterized by the presence of clinical and serological manifestations suggestive of an autoimmune connective tissue disease, but without eventual progression to a full blown specific AICTD is not unusual in clinical practice.

Keywords: Scleroderma; MCTD; SLE

Case Representation

A 24-year-old male presented to the emergency department with a history of severe abdominal pain that started suddenly and was continuous. It was associated with high grade fever, chills and an episode of vomiting. With further questioning, patient stated that 2 months prior to admission, he noticed several different skin changes on his body. These changes started as red non-itching pimples on his face, and then spread to involve the trunk, back and limbs. Later, he noted that his facial skin became tight and with time felt that it also became puffy. The skin tightening of his face lead to changes such as an inward lip retraction as if he had done plastic surgery to his face as per the patient. There was a long-term history of multiple oral ulcers, throat pain and difficulty in swallowing with a total of 5 kg weight loss within three months. Furthermore, he described a 2-years history of bluish discoloration of his fingers when exposed to cold, which he ignored, thinking it was a normal feature of his skin. On physical examination revealed obvious skin pigmentation on his face and a low-grade fever. The facial pigmentation has a distribution of malar rash sparing the nasolabial folds. There are obvious changes to his face when compared to an old photo. His nose became broad and pointed. His lips became retracted (Figure 1). He had difficult and a limited mouth opening. Oropharyngeal examination revealed three ulcers of 2 mm to 3 mm diameter in the buccal mucosa. He has scattered hairless patches on his scalp (Figure 2). There was generalized erythematous rash with old discoid lesion involving neck, trunk and back (Figure 3, 4). Patient had severe Raynaud's phenomenon resulted in digital scarring (Figure 5, 6). When asked to write his name on a paper, he had difficulty in holding the pen and writing due to stiffness of his fingers. Other systems examinations were unremarkable. His complete blood count showed a low white blood

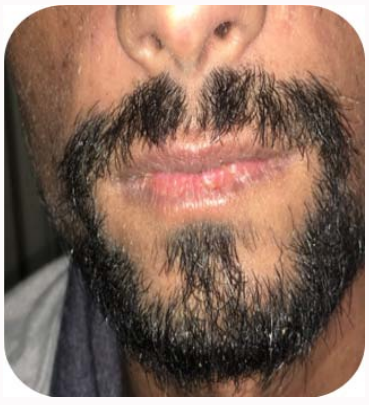

Figure 1: Retracted lips.

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Figure 2: Scattered hairless patches in the scalp.

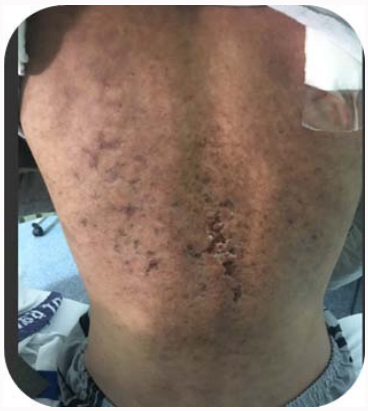

Figure 3: Erythematous macules-papules in the back.

count 3.35 × 10^9 per liter (L) and a normal hemoglobin level 12.8 g/dL with a low platelet count 80,000 × 10^9/L. The alkaline phosphatase and Gamma-Glutamyl Transferase (GGT) were elevated at 245 IU/L and 710 IU/L respectively. The Erythrocyte Sedimentation Ratio (ESR) was high 65 mm/h. The Antinuclear Antibodies (ANA) were positive 1:320 with speckled pattern. Furthermore, his serological panel showed a positive RO (SS-A), LA (SS-B), SCL-70 and Anti U1 RN. Normal renal function test and complement levels. The computed tomography of the chest showed an interstitial thickening with a multiple peripherally located bilateral faint nodules of ground glass haziness. No pleural or pericardial effusion seen with a multiple bilateral axillary as well as mediastinal lymph nodes. These findings were suggestive of non-specific interstitial pneumonia (Figure 7). The Magnetic Resonance Imaging (MRI) T2 fat suppression images of both proximal and middle thighs showed no evidence of myositis (Figure 8). Ultrasound images of kidneys showed a bilateral increased echogenicity, especially over the medullas, suggestive of a parenchymal disease. His skin biopsy showed an interface dermatitis, which was not conclusive and has a wide differential diagnosis. The transthoracic echocardiography was done to assess pulmonary artery pressure, which revealed a normal left ventricle function, normal right ventricular and pulmonary artery systolic pressure with no evidence of right sided chamber dilatation or pulmonary hypertension. The patient based on the clinical course, examination and results of laboratory results; we concluded that the patient has Mixed Connective Tissue Disease (MCTD).

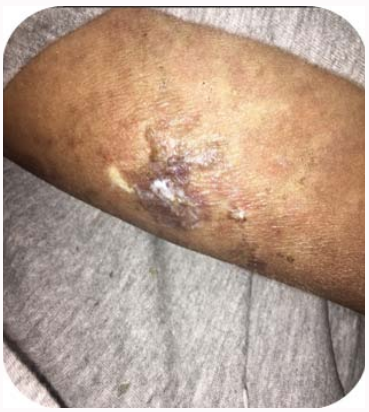

Figure 4: Cutis calcinosis.

Figure 5: Raynaud's phenomenon.

Figure 6: Digital scarring.

Discussion

Mixed Connective Tissue Disease (MCTD) is a rare connective tissue disease with an autoimmune background. It was first introduced in 1972 by Gordon C. Sharp et al. [1,2]. Sharp and Co. described MCTD as a distinct entity having a combination of clinical features of systemic lupus erythematous, scleroderma and polymyositis, with positive ENA and negative anti-SM [3,4]. However, debate still exists regarding whether MCTD is a distinct entity, or just represents an overlap syndrome of multiple connective tissue diseases or even just the early phases of an evolving, more distinct CTD [5]. MCTD

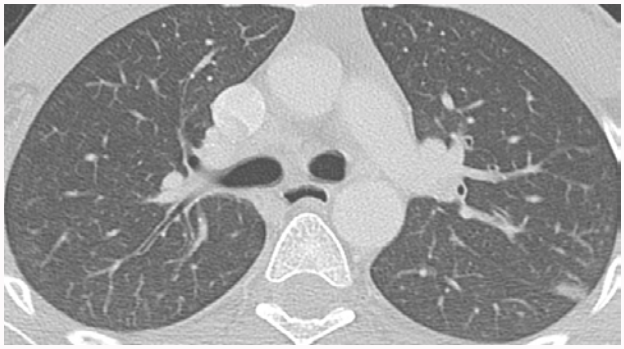

Figure 7: Computed tomography (CT) of the chest.

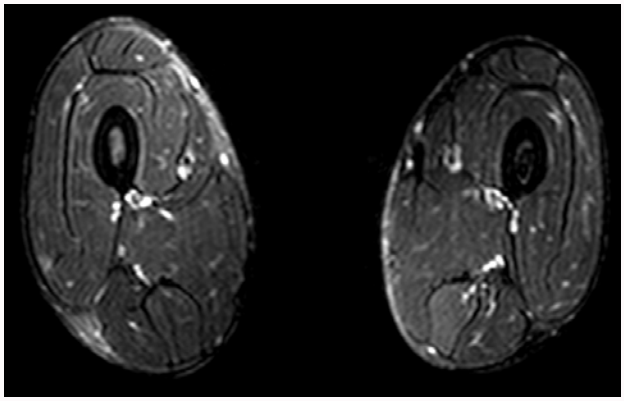

Figure 8: Magnetic resonance imaging (MRI) of the thigh.

is a rare disease. A population based study from Olmsted Country; Minnesota found that MCTD occurred in about 2 persons per 100,000 per year [6]. Studies were done in Norway and Japan revealed incidence estimated as 3.8 and 2.7 in 100,000 per year, respectively [7,8]. MCTD is more common in Females than males with a ratio of 16:1. It can occur in any age group, but most commonly initial presentation is between 15 to 25 years of age. Symptoms of MCTD develop gradually and it usually takes around 1.7 years to establish a diagnosis from the first symptom, as was shown in a study by Swart and Wolfrat [9]. Cyanosis of hand especially after exposure to cold, as in our patient, is an important warning and indicator for possible future development of CTD. That fact was introduced 30 years back by Golding, who believed that skin manifestations are involved in all cases of MCTD, with Raynaud phenomenon usually being the first [10,11]. Most common signs and symptoms of MCTD include the following with their frequency: Raynaud phenomenon (96% cumulatively, 74% at presentation), arthralgia/arthritis (96% cumulatively, 68% at presentation), esophageal hypomotility (66% cumulatively, 9% at presentation), pulmonary dysfunction (66% cumulatively, rare at presentation), swollen hands (66% cumulatively, 45% at presentation), myositis (51% cumulatively, 2% at presentation), skin rash (53% cumulatively, 13% at presentation), leukopenia (53% cumulatively, 9% at presentation), sclerodactyly (49% cumulatively, 11% at presentation), pleuritis/pericarditis (43% cumulatively, 19% at presentation), and pulmonary hypertension (23% cumulatively, rare at presentation). It is noteworthy that none of the features mentioned above are unique for MCTD, which makes establishing a diagnosis challenging, especially in the early phase. To investigate a case with suspected MCTD, most important laboratory request is an anti-U1RNP antibody by hemagglutination test, since it is highly characteristic for MCTD [12]. Other lab manifestations include anemia, leucopenia, and elevated erythrocyte sedimentation rate, hypergammaglobulinemia in 100% of patients, positive coombs test, and rheumatoid factor positive in 50% to 70% of patients. Antinuclear antibody positivity is seen in 100% of patients in high titer with coarse speckled pattern. Many patients make antibodies directed against hnRNP-A2, fibrillin-1, and nucleosomes, but not against RNA polymerases. The absence of anti-Some antibodies and anti-DNA antibodies in a seropositive patient for anti U1RNP is very important to distinguish MCTD from SLE. Antiphospholipid antibodies occur, but are less common than in those with SLE. Several criteria were set [13,14]. In all, auto antibodies were of significant value in diagnosis, management and prognosis. The presence of autoantibody to U1 small nuclear ribonucleoprotein 70 kDa, also known as U1RNP, is required. There are several classification criteria is introduced for the diagnosis of MCTD including the Sharp criteria, Alarcon-Segovia Criteria, Kasukawa Criteria and Khan Criteria. The best performance was for Alarcon-Segnovia as described by Amigus el al. [1] in 1996 with 62.5% sensitivity and 86.2% specificity [14]. Using the Alarcon-Segovia diagnostic criteria on our patient revealing a positive serology and three of the five clinical criteria were present, namely; Raynaud's phenomenon, acrosclerosis and myositis. In addition, the patient had dysphagia, skin eruption, alopecia, ulceration of distal finger parts. All of which supported the diagnosis of MCTD. Unfortunately, no control trials were done to guide the management of MCTD [15-17]. The goals of the management are to control symptoms, maintain function and prevent complications such as pulmonary hypertension. For the most common manifestation, Raynaud phenomenon, the patient should be advised to keep his hands warm and to avoid injury, smoking and caffeine. Usage of calcium channel blocker can benefit by increasing blood flow. The preferred therapeutic option for pulmonary hypertension in MCTD is prostacyclin analogs, endothelial receptor antagonist e.g. bosentan, and phosphodiesterase inhibitors e.g. sildenafil can be used [18]. Furthermore, some of the aforementioned classes can also help in the management of digital ischemic ulcers. Prognosis of MCTD depends on organs involvement. High mortality rate is related to pulmonary hypertension and interstitial lung disease. In Norwegian nationwide cohort with a mean follow-up of 5.6 years, pulmonary hypertension was responsible for approximately 25% of all deaths in patients with MCTD. A Hungarian regional cohort study revealed that a total of 50 patients developed pulmonary hypertension after a mean of 14.5 years (± 3.7 years) following the diagnosis. In addition, PAH was reported to be the major cause of mortality, causing 41% of the deaths in the study [19,20].

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