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COVID-19 Induced Mixed Connective Tissue Disease (MCTD)—Case Report

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Abstract

Mixed connective tissue disease (MCTD) is a rare systemic autoimmune disorder that damages multiple organs simultaneously and is associated with chronic inflammation, in which the signs of systemic sclerosis, systemic lupus erythematosus, and polymyositis can co-occur. Its distinctive feature and the basis for the diagnosis of MCTD is the presence of an antibody against the uridine-rich RNP of the cell nucleus (Anti-U1-RNP). It has been observed that intercurrent infections can trigger autoimmune diseases, however, the fact that viral infections—such as SARS-CoV-2—induce them is currently poorly understood. The present study raises the etiological role of the SARS-CoV-2 virus in the development of the disease. Authors describe the case of a 38-year-old patient in good general condition, who was diagnosed with mixed connective tissue disease three months after COVID-19 infection.

Keywords

Mixed Connective Tissue Disease (MCTD), Anti-U1-RNP Antibody, SARS-CoV-2, COVID-19 Infection, Post-COVID Syndrome

1. Introduction

Mixed connective tissue disease is a rare and complex autoimmune disease characterized by polyarthritis/polyarthralgia, Raynaud's phenomenon, myositis, diverse skin symptoms (e.g. photosensitivity, erythema, telangiectasias), respiratory abnormalities (interstitial lung disease, obliterative vasculopathy leading to pulmonary arterial hypertension (PAH)), gastrointestinal manifestations (e.g. oesophagus motility disorder), kidney involvement (membranous glomerulonephritis), fever and cytopaenia. The disease commonly begins between the ages of 28 - 37 and is characterized by the predominance of the female gender: 85% of patients are women [1].

The new type of coronavirus was identified in 2019, the disease it causes was named COVID-19, and it has been the protagonist of the global pandemic of the past two years. It was primarily considered to be a respiratory pathogen, but it has now become clear that it is a systemic disease due to the wide range of symptoms and organ involvements. The clinical manifestations may differ on a spectrum from asymptomatic, to mild, cold-like symptoms, to very severe, septic conditions. The acute phase can be followed by a second phase, the so-called post-COVID or long-COVID phase, which occurs in patients who have a probable or confirmed SARS-CoV-2 infection in their medical history and whose symptoms usually manifest within three months of the onset of COVID-19 and last for at least two months. The symptoms of the post-COVID syndrome cannot be explained by other, alternative diagnoses [2].

The results of several single case studies support the etiological hypothesis that respiratory pathogens can trigger the onset of autoimmune diseases [3] [4] [5]. The connection between COVID-19 and autoimmune diseases (e.g. SLE, RA, antiphospholipid syndrome) has already been suggested by numerous studies [6] [7] [8] [9], but the pathophysiology of the relationship is still unclear. This case report would like to draw attention to the possible connection between COVID-19 and MCTD.

2. Case Report

A 38-year-old female patient was diagnosed with SARS-CoV-2 infection in December 2021 after two BioNTech/Pfizer vaccinations. The patient then presented with significant weight loss, fatigue, triphased Raynaud's phenomenon, puffy fingers, in addition to inflammatory pain in her hand joints (**Figure 1**). Due to her profession (kindergarten teacher) the above symptoms significantly hindered her both at work, in her fine-motoric- and outdoor activities. In March 2022, she turned to our Post-COVID outpatient ward with her complaints. Noteworthy from her patient history was a known and treated thyroid disease requiring substitution since 2012. There was no autoimmune disease in her family.

Physical examination did not reveal any significant abnormalities. Her laboratory results showed an LDH level of 500 U/L and a creatine kinase level of 445 U/L. There was no protein excretion in the 24-hour collected urine. During the echocardiographic examination, no cardiac involvement was found, the pressure of the right side of the heart was in the normal range. Her symptoms led to the suspicion of autoimmune diseases, therefore we requested a specific immune panel, in which the rheumatoid factor, ANA screen and anti-ds-DNA gave negative, while ENA, anti-RNP A, anti-U1-RNP and anti-Sm/RNP autoantibodies gave positive results (**Table 1**). Based on her laboratory parameters and symptoms, we diagnosed mixed connective tissue disease and referred her to a rheumatology center.

Low-dose (8 mg daily initial, then 4 mg maintenance) steroid and oral hydroxychloroquine (200 mg daily) therapy was started along with pentoxyphillin

Figure 1. Raynaud's phenomenon.

Table 1. Immunospecific panel findings.

Immunospecific panel	
Reumatoid factor	13 IU/mL (reference: <14 IU/mL)
ANA PCNA (Anti-nuclear autoantibodies)	negative
Anti-RNP A	positive (+++)
Anti-U1-RNP 70	positive (+++)
ENA Sm/RNP (Autoantibodies to Extractable nuclear antigen Smith/Ribonucleoprotein)	positive (+++)
AMA-M2 (Anti-Mitochondria autoantibodies)	negative
ds-DNA (Anti-double stranded DNA autoantibody)	8.6 IU/mL (reference: <20 IU/mL)

due to her Raynaud syndrome. Abdominal ultrasound, gynecological, cardiological examinations showed no abnormalities. Ophthalmological exam showed normal Schirmer's test and break up time (BUT). Capillarymicroscopy and pulmonological examinations are still in progress. With hydroxychloroquine, 4 mg of methylprednisolone and pentoxyphillin the patient no longer has any symptoms.

3. Discussion

The diagnosis of MCTD is based on the presence of an autoantibody produced against the nuclear U1-RNP, which is characteristic to the disease and determines the symptoms. Based on the Alarcón-Segovia criteria system, the diagnosis can be made if a positive serological test and three clinical criteria (hand swelling,

Raynaud's phenomenon, synovitis, myositis, acrosclerosis) are met [10]. At the same time, other autoantibodies may also appear, varying the clinical symptoms and influencing the course of the disease, such as E-AT (anti-endothelial cell antibody), Anti-CL (anti-cardilopin antibody), Anti-CCP (anti-cyclic citrullinated peptide antibody) [11].

The Department of Clinical Immunology of the University of Debrecen processed the data of their patients they cared for and divided them into 3 subgroups. In group Number 1 number vascular abnormalities dominated (PAH, Raynaud's, etc.), the background of which is attributed to E-AT in addition to Anti-U1-RNP. In group Number 2, interstitial respiratory disease, myositis and oesophageal motility disorder occurred significantly higher than in the other two groups. During lung biopsy analyses, IgM-type immunoglobulin deposits were found in the alveolar epithelial cells. In group Number 3, erosive arthritis was the characteristic symptom of the disease. In this group anti-CCP antibodies were detected in these patients in addition to anti-U1-RNP. Overall, the above signifies the importance of the detection of autoantibodies, as they determine the type of organ abnormalities and thus the necessary therapy and screening [12].

Treatment of patients with MCTD depends on the symptoms, organ involvement and disease activity [13]. Already in the 1980s, it was recognized that the disease is much less benign than previously considered, as the severe involvement of the vessels of the connective tissues leads to significant parenchymal damage [14]. In MCTD, pulmonary arterial hypertension (PAH) develops between 23% - 50% of the cases, often manifesting in a rapid and progressive form, which may lead to sudden death [15]. Based on histopathological samples, PAH ranks first among the causes of death associated with MCTD and accounts for half of the deaths in affected patients [16]. The above enhances the importance of early diagnosis and timely treatment: immunosuppressive treatment that reduces endothelial cell proliferation and the production of inflammatory mediators (cyclophosphamide, corticosteroid), as well as the administration of prostacyclin therapy and endothelin receptor blockers. Furthermore, the follow-up of diagnosed patients is of particular importance, regular echocardiographic control with measurement of pulmonary pressure [17].

Interstitial respiratory disease (ILD), which is caused by the inflammatory parenchymal damage of the lung, is another disease that greatly determines the life expectancy of the patient as it generally results in poor outcomes. It manifests in approximately 20% - 65% of MCTD patients. At the same time, in the presence of Anti-U1-RNP autoantibody, nephritis occurs significantly less frequently than in Anti-DNA positive SLE patients [18].

Raynaud's phenomenon, which was previously considered benign for a long time—and can be observed in 75% - 90% of MCTD patients—capillary microscopy clearly proves that the background is not only vasospasm, but damage and fragmentation of the capillary endothelium. Giant capillaries and bushy capillaries are characteristic in MCTD. In other words, the vasospasms initially provoked by cold or stress become permanent over time, and cause permanent dam-

age in the vascular system leading to worsening pain in the extremities later followed by digital ulceration and trophic disorders [19].

4. Conclusions

In our case report, we present the case of young, previously healthy female patient with confirmed COVID-19 infection, who developed Raynaud's phenomenon after the infection. Detailed examinations and evaluation lead to the diagnosis of MCTD. Taking the type of autoantibodies detectable in the patient into consideration, it can be stated that our patient belongs to group 1 of the Debrecen classification with dominant vascular involvement, therefore cardiology and pulmonology follow-ups are essential in order to avoid potentially fatal complications.

MCTD is one of the chronic autoimmune entities. Its development can be triggered by COVID-19. MCTD is a rare disease in itself, and no case reports have been published in connection with a COVID-19 infection until now.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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