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CASE REPORT

Mixed Connective Tissue Disease (MCTD) in a Girl with Lower Extremities Edema: A Brief Report

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Abstract: ***Background*:** Mixed Connective Tissue Disease (MCTD) is a rare condition in children, characterized by a high titer of anti-ribonucleoprotein-U1 (anti-U1 RNP) antibodies, often presenting with overlapping features of two or more rheumatologic disorders, including juvenile idiopathic arthritis (JIA), systemic lupus erythematous (SLE), systemic sclerosis (SSc), and juvenile dermatomyositis/polymyositis (JDM/PM).

***Case Presentation*:** We report the case of an 8-year-old girl with a history of fever, hair loss, lower extremities edema, weakness, oral aphthous ulcers, and a high titer of anti-U1 RNP antibodies, which is consistent with the diagnosis of MCTD. The patient received immunomodulator drugs, and her disease went into remission.

***Conclusion*:** Diagnosing MCTD in pediatric patients can be challenging. It should be considered especially in cases with recurrent muscular weakness or pain, lupus-like manifestations, and edema. Moreover, serum anti-U1 RNP testing can be a helpful diagnostic tool.

Keywords: Children, RNP, Edema, MCTD, SLE, JDM, JIA.

1. INTRODUCTION

Mixed connective tissue disease (MCTD) is an exceedingly rare form of systemic autoimmune disease recognized by the development of high titer autoantibodies directed against U1-ribonucleoprotein (RNP) [1, 2]. Clinically, it is characterized by the overlap of two or more rheumatologic disorders, including juvenile polymyositis/dermatomyositis, systemic sclerosis, juvenile idiopathic arthritis (JIA), and systemic lupus erythematosus (SLE). In children with MCTD, the most frequent clinical symptoms are polyarthritis/polyarthralgia, Raynaud's phenomenon, and myositis. Clinical signs of dermatomyositis, SLE, or JIA may be the initial presentations of MCTD [3, 4]. None of the former classification criteria related to MCTD, including Kasukawa's, Alarcon-Segovia's, Khan's, and Sharp's criteria, have been accredited for pediatrics (Table **1**). Due to the absence of validated criteria for children, adult criteria have been used to diagnose MCTD in this age group. While the presence of Anti-Sm antibodies is a criterion for exclusion in Sharp's criteria, it may coexist with other differences in some pediatric patients [4]. MCTD is a rare disease during childhood, with a prevalence of 0.3-0.6% among American pediatric patients with rheumatic diseases and a female-to-male ratio of 6:1. Nearly one-fifth of cases manifest in children, with a mean age of 11 years old [5]. Although there are no unique signs or symptoms in the rudimental stages of the disease, Raynaud's phenomenon (RP), malaise, arthralgia, myalgia, and fever are possible early symptoms. The symptoms of the disease evolve over time, with a mean duration from the initial symptoms up to diagnosis reported to be between 1.7 to 2 years. There are some oral manifestations of MCTD, such as a fissured tongue or dental decay [6, 7]. The serological clues are high titers of Anti-nuclear and RNP antibodies, followed by the rheumatic factor (RF) (68-70%) and anti-dsDNA (20-40%). However, anti-U1 RNP antibodies are more exclusive for the diagnosis of MCTD [8]. In this report, we aimed to present the case of an 8-year-old girl with the final diagnosis of MCTD.

2. CASE PRESENTATION

An 8-year-old girl was referred to Mofid Hospital, located in Tehran, Iran, with a history of intermittent fever, cutaneous rashes, photosensitivity, hair loss, oral aphthous ulcers, weakness, lower extremity edema, and weight loss that

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Table 1. Classification Criteria for MCTD.

Classification Criteria	Serological Criteria	Clinical Criteria	Diagnosis
Iarcon-Segovia (1987)	anti U1 RNP titer >1:1600	a. Hands or fingers edema b. Synovial inflammation c. Myositis d. Raynaud´s phenomenon e. Acrosclerosis	Serological criteria and ≥3 clinical features included synovial inflammation or myositis
Kusukawa (1987)	Common Symptoms Raynaud´s Phenomenon Swollen hands or fingers Positive Anti U1 RNP	Mixed findings A. Lupus-like: Polyarthritis Pericarditis/pleuritis Lymphadenopathy Erythema of face Thrombocytopenia/ Leucopenia B. Scleroderma-like: Sclerodactyly Lung fibrosis Esophageal dysmotility C. Polymyositis-like Muscle weakness High creatine-phosphokinase Myopathic electromyogram	≥ one common symptom, with positive U1 RNP and one or more findings in ≥ two of the three categories A, B, and C.
Sharp (1987)	Major Criteria a1. Severe Myositis 2. Lung (respiratory) involvement a. CO-diffusing capacity < 70% b. Pulmonary arterial hypertension c. Proliferative vascular lesions in pulmonary biopsy 3. Esophageal hypo-motility or Raynaud's phenomenon 4. Swollen fingers or sclerordactyly 5. Highest anti-ENA≥1:10,000 and positive anti U1 RNP and negative anti-Sm.	Minor Criteria: 1. Alopecia 2. WBC <4,000 /mm3 3. Hb ≤10.0 g/dL in females, and <12.0 g/dL in males 4. Pleuritis 5. Pericarditis 6. Arthritis 7. Trigeminal neuropathy 8. Malar rash 9. Platelet count <100,000/mm3 10. Mild myositis 11. Puffy hands	4 major criteria, and positive anti-U1 RNP, with anti-ENA ≥1:4000. Exclusion: anti-Sm Probable 3 major criteria and anti-positive U1 RNP with anti ENA ≥1.1000 2 major criteria (including 1 or more from #1, #2, #3 and 2 minor criteria, and positive U1 RNP with anti- ENA ≥1.1000) 3 major criteria Possible 2 major criteria and positive U1 RNP with anti-ENA ≥1:100 1 major and 3 minor, and positive U1 RNP with anti-ENA ≥1:100
Khan	Serological criteria: Positive anti-RNP (U1 68kd) anti-RNP ≥ 1/2000	Clinical criteria: 1. Raynaud's phenomenon (The obligatory criterion) 2. Synovitis 3. Myositis 4. Swollen hands	Serological criteria, and ≥3 clinical criteria

occurred gradually over the previous year. The parents were first-degree relatives, and there was a history of three miscarriages in her mother. Her grandmother had been suffering from Rheumatoid Arthritis for 25 years. She has been treated several times with hydroxychloroquine (200 mg/day) and prednisolone (5 mg/day) without definite diagnosis. She underwent a complete examination while experiencing illness, thinness, arthralgia, myalgia, and general weakness at that time. Vital signs at the first visit, including blood pressure, temperature, pulse rate, and respiratory rate, were 100/70 mm. Hg, 36.5°C, 85 beats/min, and 18 beats/min, respectively. She appeared ill and pale in general, with malar rash, heliotrope rash, puffiness of hands, lower extremity edema (up to the knees), and oral aphthous ulcers in several parts of the oral cavity (Fig. **1**). There was decreased bilateral muscle strength in both upper and lower extremities (three out of five in the upper and four out of five in the lower extremities). There was no organomegaly on the abdominal examination, and the chest examination was normal. The patient was admitted, and laboratory examination, abdominopelvic ultrasonography, chest X-ray, chest computed tomography (CT) scan, Magnetic Resonance Imaging (MRI) of the femur, electromyography-Nerve conduction Velocity (EMG-NCV), and bone marrow aspiration were all performed.

Fig. (1). A). Malar Rash, **B).** Foot, and Leg Edema. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

Additionally, immunologic, pulmonologic, ophthalmologic, and cardiac consultations were carried out. The ophthalmologist reported a mild cataract. The main Laboratory and immunologic data are summarized in Table **2**. Chest X-ray was normal. Abdominal ultrasonography revealed a normal liver size with increased echogenicity. Mild splenomegaly (95 mm) was noted. In the chest Spiral CT scan, there were scattered parenchymal nodules up to 5 mm in both lungs, and the possibility of fungal infection was suggested. In the femoral MRI, there were abnormal signals and inflammatory changes in the subcutaneous tissues of the bilateral gluteus and bilateral thighs, along with abnormal signals in the deep fascias of the posterior compartment of the thighs. Patchy abnormal signal changes in quadriceps muscles were seen along with atrophic changes and abnormal high signal intensity in bilateral gluteal muscles, especially on the left side. In EMG-NCV, a myopathy process involving all limbs in proximal muscles, accompanied by spontaneous activity in upper limbs and Para spinal muscles, was observed. There was no evidence of motor neuron disease or polyneuropathy in any limbs; however, an inflammatory process was seen. The ANAs, Complements, Anti-Ro, and Anti-Topoisomerase-I antibodies were negative, while Anti-ds DNA, RF, and U1 RNP were positive. Based on clinical manifestations and the presence of a high titer of anti-U1 RNP, the diagnosis of MCTD was confirmed.

The treatment was initiated for the patient with intravenous methylprednisolone pulse (30 mg/kg) in three doses for three days. Then, it was switched to oral methylprednisolone at 2mg/kg for the following three days. After that, she received prednisolone (2 mg/kg) twice a day. Additionally, Hydroxychloroquine (7 mg/kg/day) and Mycophenolate Mofetil (500 mg) were administrated twice a day. The patient experienced remission after nearly 14 days. She was followed up for at least six months, showing good clinical and para-clinical examination results.

Table 2. Laboratory data.

Laboratory Parameter	Day-1 and 14	Laboratory Parameter	Day-1 and 14
WBC (4.5-5 *10^9)	5 -4.3	ESR	39-43
Hb (>12 g/dL)	10.4 -9.5	CRP	1-9
Plt (>150*10^6)	310 -358	Ig G	1157-1138 (normal)
MCV	90.4-91.7	Ig M	221-228 (high)
Neutrophil (%)	58 -62.5	Ig A	205-197 (normal)
Lymph (%)	35 -31.1	Ig E	121-122 (normal)
VitD3	11	HCV Ab, HBS (Ag and Ab)	Negative
CPK	34	U/A	Normal
Cr	0.63	Urine vlume24h=1900 (600-2500) •Urine protein 24h=228(20-150) •Urine Cr 24h =376	
ALT	46		
C3, C4, CH50	NL		
RF	++	ANA/FANA	Negative/1/160
Total protein	5.8	EBV PCR	Negative
Mg	2	Paraviruses-B19 DNA	Negative
Albumin (>3 g)	4.2	CMV DNA PCR	Negative
Anti JO-1	Negative	Cortisol	Negative
SS-A Ab	Negative	Anti CCP	Negative
Anti SCL-70	Negative	Calprotectin	Negative
ds DNA Ab	Positive (54)	Anti cardiolipin (IgG & IgM)	Negative
Anti SCL-70	Negative	Lupus anti-coagulant	Negative
Anti-U1 RNP	Positive	B2-Glycoprotein (IgG & IgM)	Negative

3. DISCUSSION

MCTD is a scarce form of systemic autoimmune disease that shares characteristics with two or more connective tissue diseases (CTD), including systemic lupus erythematosus (SLE), dermatomyositis (DM)/ polymyositis (PM), systemic sclerosis (SSc), and rheumatoid arthritis (RA). Additionally, it is characterized by finding a distinct antibody known as anti-U1- ribonucleoprotein (RNP) [3, 4]. In our case, we observed the presence of SLE and juvenile DM features, such as malar rashes, photosensitivity, and proximal muscle weakness. She also exhibited hand puffiness and extensive leg edema at the time of presentation. Furthermore, we identified a critical laboratory finding of MCTD: the presence of anti-U1 RNP antibody. RF was also detected to be positive in this patient. Various autoantibodies, including RF, Anti-Ro, and ds DNA, may be present, along with strong antinuclear antibodies (ANAs) [3, 5]. A picture of polyarthritis, general malaise, and Raynaud's phenomenon represents the most typical presentation of childhood MCTD, all of which were present in our patient. Patients may also exhibit telangiectasia, lymphadenopathy, alopecia, rash, and proximal muscle weakness. A comprehensive physical examination is essential to identify silent or mild symptoms, such as rashes, oral symptoms, and other non-criterial symptoms. Clinical examination and diagnostic procedures are used as classification factors, in addition to autoantibody status. Physical examination may reveal the presence of alopecia, pleuritic chest pain, pericardial rub, arthritis, Raynaud phenomenon, malar rash, petechial rash, muscle weakness, swollen hands, and acro-sclerosis or sclera-dermatoses skin changes [1]. However, the symptoms in children may differ from those in adults. Due to the absence of definite criteria for diagnosing pediatric-onset MCTD, four current diagnostic criteria are employed. According to Sharp's criteria, a diagnosis of MCTD is confirmed when four major criteria are met, including the highest anti-U1 RNP (more than1:10,000) with negative anti-Sm antibodies, severe myositis, pulmonary involvement (diffusing lung capacity for carbon monoxide 70% of normal, proliferating vascular lesions, pulmonary hypertension, Raynaud's phenomenon, esophageal hypo-motility, swollen hands, and sclera-dactyly). Based on Alarcon-Segovia and Villareal criteria, for a definite MCTD diagnosis, the patient must have a positive anti-RNP (1:1600 or higher) and at least three clinical manifestations, such as edema of the hands, Raynaud's phenomenon, acro-sclerosis, synovitis, and myositis or its laboratory manifestations [9-12]. In a recent systematic review conducted in Italy in 2023, all manifestations, including both criterial and non-criterial manifestations of pediatric-onset MCTD patients, were evaluated. When indicated, the most common criteria for diagnosis were Kasukawa, Alarcon-Segovia, and Sharp's criteria, respectively. This review did not find any studies using the Khan criteria. From 1973 to 2019, a total of 218 pediatric patients were included. The majority were girls (81.5%), and the mean age at onset was 147 months. Joint involvement, Raynaud's phenomenon, myositis, and swollen fingers/hands were the most common features. Dermatologic signs were found to be heterogeneous and common, affecting one-third of patients. Fever, not covered by any criteria, was noted in one-fourth of cases. Pulmonary and esophageal involvement were reported in a lower percentage at the onset, indicating a more developmental nature of these conditions [13]. Our patient had a fever, rashes, edema, muscular abnormality in MRI, Chest abnormalities, Raynaud's phenomenon, and a positive anti-U1 RNP that were compatible with the diagnosis. After receiving treatment, our patient experienced a significant remission in her symptoms, and in follow-ups, she did not experience a flare-up with the treatment. Pediatric MCTD is not specifically treated. However, for mild to severe symptoms, nonsteroidal anti-inflammatory medicines, anti-malaria medications like Hydroxychloroquine, and corticosteroids are the preferred treatments. If internal organs, such as the kidneys and central nervous system, are affected, immunosuppressant agents, such as cyclophosphamide, are necessary [7, 14]. To maintain the condition in remission, our patient received treatment with hydroxychloroquine and high-dose corticosteroids. However, some patients with MCTD may have a poor prognosis, particularly if they develop pulmonary hypertension, do not receive treatment, experience renal involvement like glomerulonephritis, or have neurological involvement, according to numerous studies. Some studies found that mortality rates ranged from 16% to 28%. A more recent study discovered that while adult mortality is 12-23 per 1000 patients, juvenile mortality is lower, near 3-4 per 1000. Cardiovascular involvement and pulmonary hypertension are the most frequent causes of death [1, 2, 6, 15]. However, our case had chest involvement, which has been reported in several reports, especially as a late presentation [4, 13]. She experienced fever, which is found in one-quarter of patients. The lower extremity edema was so impressive that it was not compatible with the current hand or foot puffiness.

CONCLUSION

MCTD in pediatrics should be considered, especially in pediatric patients with Raynaud's phenomenon, recurrent muscular weakness or pain, lupus-like manifestations, and edema. This disease can be managed with anti-inflammatory and immunomodulatory agents but has no cure. Moreover, anti-U1 RNP is generally known as a serological marker that should be checked.

LIST OF ABBREVIATIONS

ANA	=	Antinuclear Antibody
anti-U1 RNP	=	Anti-ribonucleoprotein-U1
CT	=	Computed Tomography
CTD	=	Connective Tissue Diseases
DM	=	Dermatomyositis
EMG-NCV	=	Electromyography-Nerve Conduction Velocity
JIA	=	Juvenile Idiopathic Arthritis
MCTD	=	Mixed Connective Tissue Disease
MRI	=	Magnetic Resonance Imaging
PM	=	Polymyositis
RA	=	Rheumatoid Arthritis

RNP = U1-ribonucleoprotein

SLE = Systemic Lupus Erythematosus

SSc = Systemic Sclerosis

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The study was approved by the Ethics Committee of Iran University of Medical Sciences (IR.IUMS.FMD.REC. 1397.256).

HUMAN AND ANIMAL RIGHTS

All human procedure were followed in accordance with the guidelines of Helsinki Declaration.

CONSENT FOR PUBLICATION

Informed consent was received from the guardian.

STANDARDS OF REPORTING

Care guidelines were followed in this study.

AVAILABILITY OF DATA AND MATERIALS

The data supporting the results and findings of this study are available within the article.

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None.

CONFLICT OF INTEREST

The authors declared no conflict of interest, financial or otherwise.

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