—Case Reports—

Use of Tocilizumab to Treat Arthritis Associated with Mixed Connective Tissue Disease Complicated by Ovarian Teratoma: A Case Report

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Mixed connective tissue disease (MCTD) is characterized by mixed features of systemic lupus erythematosus, systemic sclerosis, and polymyositis/dermatomyositis and is rare in children. Here, we report a case of MCTD in a 10-year-old girl who presented at our hospital with arthralgia, Raynaud's phenomenon, and fatigue. Blood tests were positive for anti-U1-ribonucleoprotein (RNP) antibodies and for rheumatoid factors (RFs) IgG-RF and anti-galactose-deficient IgG. Levels of myogenic enzymes and hypergammaglobulinemia were elevated. Macrophages were prominent in bone marrow, with scattered phagocytic macrophages. MCTD was diagnosed based on the patient's symptoms and laboratory findings. Methylprednisolone pulse therapy combined with oral tacrolimus was administered, which led to resolution of symptoms. Three months after pulse therapy, arthralgia worsened and methotrexate was administered. Arthralgia improved but did not resolve. Magnetic resonance imaging performed to investigate the hip pain revealed a mature ovarian teratoma, which was surgically removed. Because the pain persisted and interfered with her daily life, she was treated with tocilizumab for joint pain relief, which decreased the pain level. Tocilizumab is a candidate for additional treatment of juvenile idiopathic arthritis-like arthritis associated with childhood-onset MCTD.
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Key words: mixed connective tissue disease, MCTD, tocilizumab, ovarian teratoma

Introduction

Mixed connective tissue disease (MCTD) is a disorder that combines the symptoms of systemic lupus erythematosus, systemic sclerosis, and polymyositis/dermatomyositis[1], which may be observed at disease onset or during its course. Not all symptoms of the three diseases are always present. MCTD is characterized by Raynaud's phenomenon and the presence of anti-U1-RNP antibodies in the blood. The number of pediatric patients with MCTD is very low—0.33 per 100,000 children in Japan[2]—and only 2% of pediatric patients with rheumatic disease have MCTD in Japan[3]. Recent studies reported an association between autoimmune diseases and tumors, but few have focused on MCTD. We report a case of a 10-year-girl with MCTD complicated by an ovarian teratoma and with positive test results for three rheumatoid factors. Arthralgia persisted after multidrug therapy but improved with additional administration of tocilizumab.

Case Report

A 10-year-old girl was admitted to our hospital with joint swelling and pain in both hands, morning stiffness, abdominal pain, headache, weakness, rash, dyspnea with light exertion, generalized itching, and a 5-kg weight loss

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Table 1 Laboratory data on admission

WBC	7,090 /μL	IgG	2,305 mg/dL	IL-6	22.4 pg/mL
Neut	69.3 %	IgA	81 mg/dL	MMP-3	25.9 ng/mL
Lym	17.1 %	IgM	74 mg/dL	RF	116 IU/mL
Hb	13.8 g/dL	CH50	42 U/mL	anti-CCP	negative
Plt	38.5 ×/10⁴μL	C3	158 mg/dL	IgG-RF	3.1
		C4	23.1 mg/dL	anti-agalactosyl IgG	139.1 AU/mL
TP	7.9 g/dL	ANA	5,120 × (speckled)	IL-2R	2,556 U/mL
Alb	3.7 g/dL	anti-U1-RNP	113.7 U/mL	KL-6	373 U/mL
BUN	6.1 mg/dL	anti-Sm	negative		
Cre	0.28 mg/dL	anti-ds-DNA	negative		
Na	141 mEq/L	anti-ARS	negative		
K	4.7 mEq/L	anti-MDA-5	negative		
Cl	106 mEq/L	anti-TIF1γ	negative		
LDH	570 U/L	anti-Mi-2	negative		
AST	123 U/L	anti-Jo-1	negative		
ALT	67 U/L	anti-SS-A	negative		
CK	1,703 U/L	anti-Scl-70	negative		
aldolase	104.2 U/L	anti-polymerase	negative		
CRP	0.05 mg/dL				

ANA: anti-nuclear antibody; anti-U1-RNP: anti-U1-ribonucleoprotein antibody; anti-Sm: anti-Smith antibody; anti-ds-DNA: anti-double stranded DNA antibody; anti-ARS: anti-aminoacyl-tRNA synthetase antibody; anti-MDA-5: anti-melanoma differentiation-associated gene 5 antibody; anti-TIF1γ: transcription intermediary factor 1-γ; anti-Scl-70: anti-scleroderma antibody; IL-6: interleukin-6; MMP-3: matrix metalloproteinase-3; RF: rheumatoid factor; anti-CCP: anti-cyclic citrullinated peptide antibody; IL-2R: interleukin-2 receptor; KL-6: sialylated carbohydrate antigen KL-6

over several months.

On examination, her height was 146 cm, weight was 43 kg, temperature was 37.0°C, and blood pressure was 105/75 mm Hg. Erythema was observed in the cheeks. Skin findings characteristic of dermatomyositis, such as Gottron's sign and heliotrope rash, were not observed. Raynaud's phenomenon and arthralgia were observed in her fingers. Eighteen of the 20 metacarpophalangeal joints were tender, swollen, and hot, and 5-7 of the 20 proximal interphalangeal joints were tender. The JADAS-27 score was 26. No abnormalities were observed in the thorax or abdomen.

Blood testing revealed elevated levels of myogenic enzymes (**Table 1**) and hypergammaglobulinemia. The results of tests for anti-U1-RNP antibodies and RFs (IgG-RF and anti-agalactosyl IgG antibody) were positive. Tests for autoantibodies for dermatomyositis and scleroderma and antibodies for anti-dsDNA and anti-Sm yielded negative results, and complement levels were not decreased. No leukopenia or thrombocytopenia was observed. Urinalysis revealed no abnormalities.

Bone radiography of the hands, and chest computed tomography, revealed no abnormal findings. MRI of the thighs showed fat-suppressed images with high pale signals in multiple muscles, including the biceps femoris, indicating myositis. Electrocardiography and echocardiography revealed no abnormalities, and respiratory examination results were normal. The cold stimulation test showed a biphasic change from pallor to red, thus confirming Raynaud's phenomenon. Macrophages were prominent in a bone marrow aspiration smear, with scattered phagocytic macrophages. The blood test results did not meet the diagnostic criteria for macrophage activation syndrome. Bone density was measured by lumbar spine dual-energy X-ray absorptiometry (L2-L4), and the Z-score was −2.3, indicating reduced bone density. The symptoms and laboratory findings met the revised diagnostic criteria (2021) for MCTD[4]; thus, the patient was diagnosed as having MCTD.

Initial treatment consisted of methylprednisolone pulse therapy (MPT) administered as induction therapy to control the onset of fever, arthritis, and myositis symptoms. mPSL was administered at 1 g/day for three courses. Tacrolimus (TAC) was added on the basis of bone marrow examination findings. After MPT, fever resolved and arthralgia decreased (**Fig. 1**). Alendronic acid was administered to prevent loss of bone minerals.

Prednisolone (PSL) was tapered off after discharge, but 3 months after discharge, the patient experienced worsening arthralgia. Pelvic MRI showed no evidence of in-

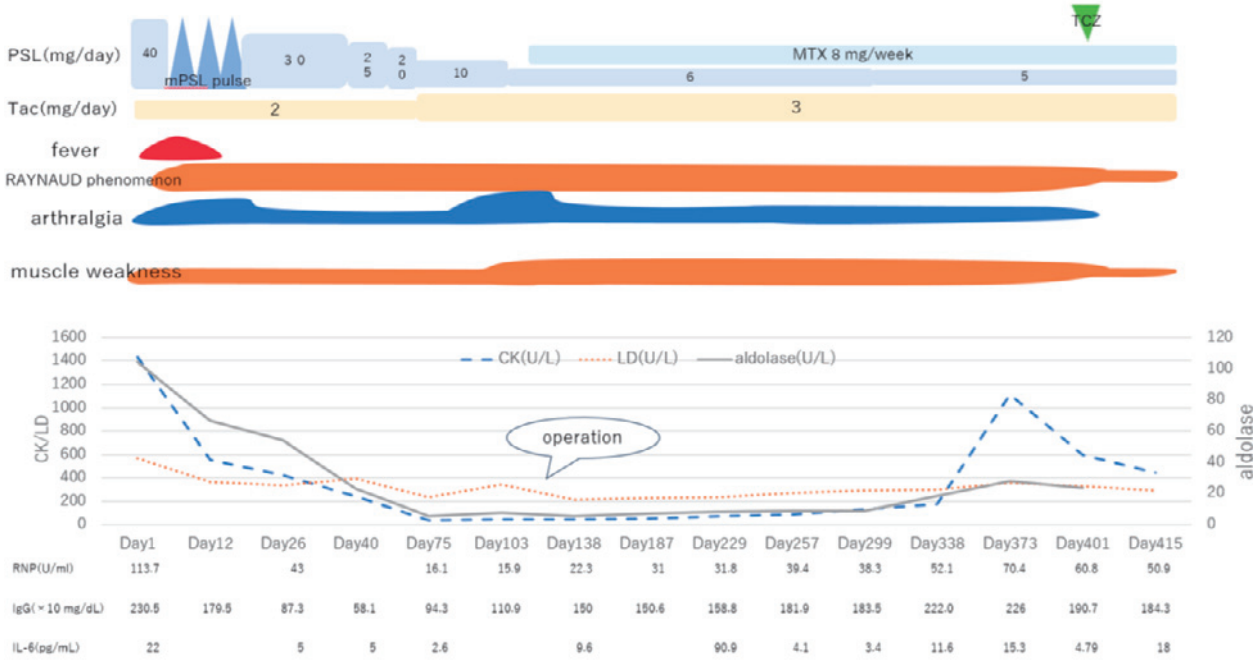

Fig. 1 Clinical course.

flammation in the hip joint; however, an ovarian cyst was discovered and surgically removed. Pathological examination confirmed the diagnosis of a mature ovarian teratoma (**Fig. 2** and **Fig. 3**). Arthralgia was relieved after starting methotrexate (MTX), although pain persisted. One week after forgetting to take MTX, the pain worsened, confirming that MTX suppressed her pain. The pain persisted and interfered with school activities. Additional time was required for general movement, and she had difficulty turning on the water tap, could not hold rags during cleaning, and could not perform lunch duties. Joint pain and muscle weakness made participation in school activities difficult. Restrictions on physical movement also limited her ability to attend school. Therefore, tocilizumab was administered intravenously every 4 weeks to reduce joint pain. A decrease in pain was observed after administering the first dose.

This report does not include any clinical studies involving human or animal subjects. Written informed consent for the publication of this case report was obtained from both the patient and her parents.

Discussion

Evidence regarding treatment of pediatric MCTD is limited. Treatment is in accordance with guidelines for SLE, SSc, and PM/DM and the patient's condition. In our case, onset was early but bone destruction was not observed on X-ray. Although arthritis is observed in SLE, our patient tested negative for anti-dsDNA antibodies, making SLE unlikely. In a report by Fujii et al.[5] on the use of tocilizumab for pediatric MCTD, the patient tested positive for RFs at onset; however, 3 years after the onset of Raynaud's symptoms, he tested negative for anti-CCP antibody and had elevated MMP-3 levels; arthroscopy showed villous synovial hyperplasia. Cabrera et al.[6] used tocilizumab to treat a 7-year-old girl with MCTD and a 12-year-old girl with overlap syndrome and reported its effects on arthritis. Despite the use of both methotrexate and prograf, the patient's life was limited by pain. In our case, tocilizumab was added to the regimen, and a reduction in pain was observed after the first dose. Cyclophosphamide pulse therapy is used in pediatric MCTD, although it has serious side effects, including infertility and malignancy. In our patient with ovarian teratoma, we opted against using cyclophosphamide, to minimize the risk of infertility and secondary malignancy.

Arthritis is the second most common symptom (94%) of MCTD after Raynaud's phenomenon (100%)[7]; however, no clear treatment criteria have been established. Previous studies indicated that interleukin (IL)-6 is involved in the pathogenesis of arthritis in MCTD[8]. In addition, although the diagnostic criteria for sJIA were not met in the present case, the patient was positive for rheumatoid factor and elevated IL-6 and ferritin, which we consider an aspect of sJIA. The improvement in joint pain after additional TCZ treatment alleviated the limita-

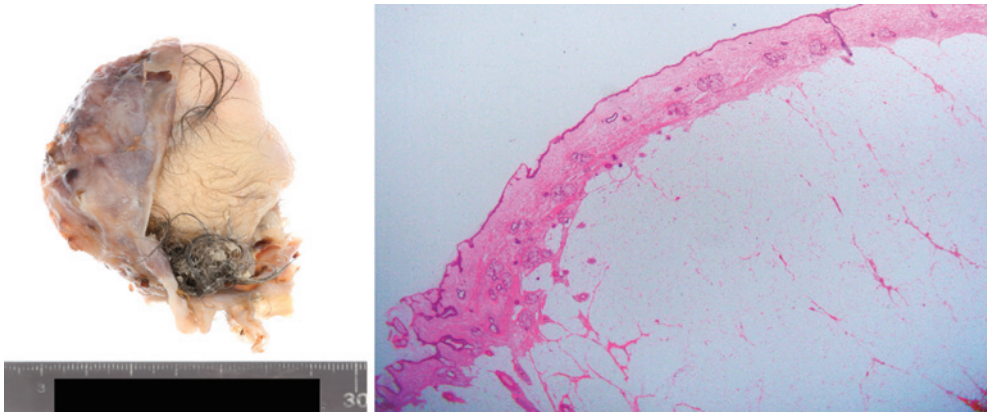

Fig. 2 Extracted specimen.
Grossly, it is a monocystic cystic mass approximately 6.5 × 5.5 cm in size, with an interior filled with fat, hair, and bone tissue. The superficial layer of the cystic mass is covered with an epidermal-like keratinized stratified squamous epithelium containing abundant adipose tissue. There is no evidence of dermatomyositis or scleroderma.

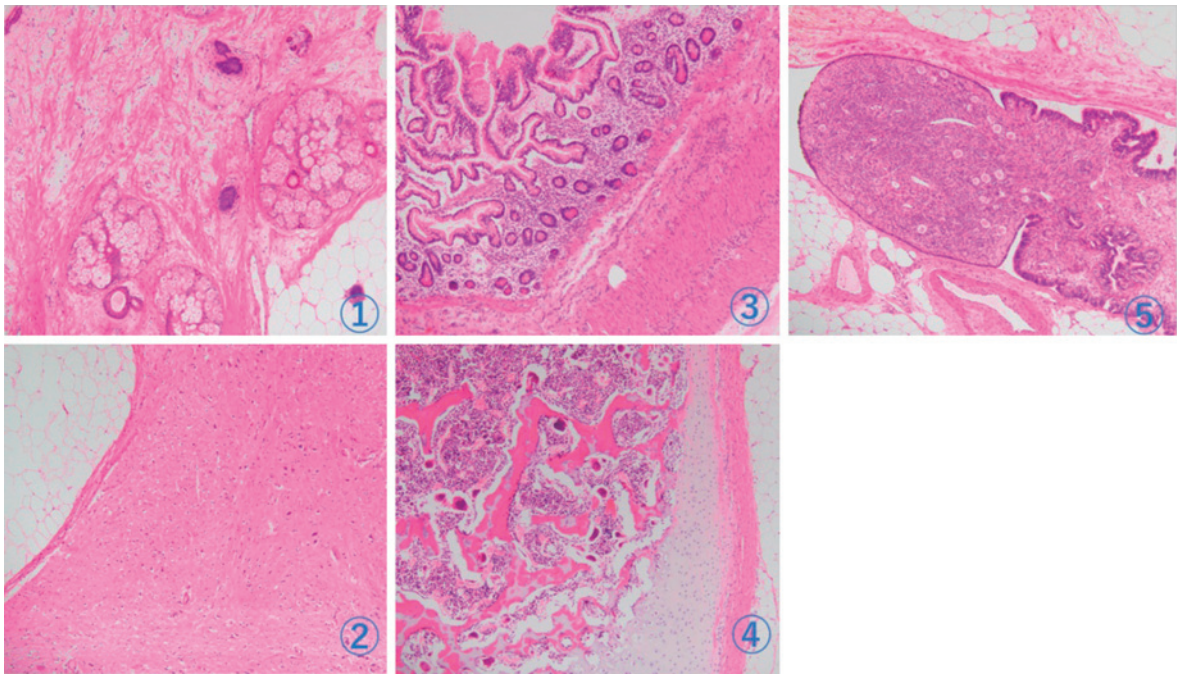

Fig. 3 Histopathological examination.
① Deformed sebaceous glands and hair follicles.
② Neurons and glial cells mimic the central nervous system.
③ Structure mimicking the mucosa of the small intestine.
④ Cartilage and bone tissues are observed, with involvement of the bone marrow tissue.
⑤ Ovarian tissue with follicles and oviduct-like structures are also observed within the teratoma.

tions in daily living, and bone mineral density loss was observed immediately after starting PSL; however, both long-term steroid administration and MCTD may be associated with bone loss[9]. Thus, evaluations should be conducted with a focus on secondary osteoporosis. A careful search for complications, including screening for pulmonary hypertension, which is considered to have the greatest impact on prognosis, should be continued.

Many collagen diseases, especially dermatomyositis, are associated with tumor development, and the frequency of complications by malignant tumors, such as ovarian and lung cancer, is high[10]. However, few reports have focused on MCTD and, to our knowledge, no case of childhood MCTD complicated by tumors has been re-

ported. In a previous report, a 10-year-old girl with musculoskeletal symptoms and high anti-RNP antibody levels was diagnosed with metastatic undifferentiated carcinoma of an unknown primary site and tested negative for RNP antibody after chemotherapy[11], suggesting a relationship between anti-RNP antibodies and tumor development. It is possible that this case is tumor-associated rheumatic disease caused by antibodies cross-reacting with tumor cells or autoantigens, but the patient's symptoms did not improve after surgery, making tumor-associated rheumatic disease unlikely in this case. However, childhood-onset ovarian teratomas often develop contralaterally or recur[12] and should continue to be screened for using tumor markers and imaging evaluations. A careful search for complications, including screening for pulmonary hypertension, which has the greatest impact on prognosis, should also be continued.

Conclusion

Here, we report a case of mixed connective tissue arthritis complicated by ovarian teratoma in a pediatric patient who responded well to tocilizumab. Few cases of pediatric MCTD have been reported, and the course of treatment remains unclear. To alleviate symptoms, new treatment options should be selected empirically.

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Conflict of Interest: The authors declare no conflict of interest.

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