Korean Journal of Pediatrics Vol. 51, No. 8, 2008
DOI : 10.3345/kjp.2008.51.8.886
Case report

A case of mixed connective tissue disease presenting initially with Raynaud's phenomenon

Soo Young Kim, M.D., Young Seok Choi, M.D.,
Young Ok Kim, M.D., and Young Jong Woo, M.D.

Department of Pediatrics, School of Medicine, Chonnam National University, Gwangju, Korea

= Abstract =

Mixed connective tissue disease (MCTD) is characterized by diverse symptoms including rheumatoid arthritis, scleroderma, systemic lupus erythematosus, and dermatomyositis, associated with high titers of antibodies to extractable nuclear antigen (ENA), especially anti-ribonucleoprotein (anti-RNP) antibody. Since the first report of 25 cases with MCTD in adults, there have been only a few cases of MCTD reported in children. Here, we report a rare childhood case of MCTD in a 7-year-old girl presenting initially with Raynaud's phenomenon, swollen hands, and ulceration of the right index finger tip followed by alopecia and arthritis during follow-up. **(Korean J Pediatr 2008;51:886-891)**

Key Words : Mixed connective tissue disease, Raynaud's phenomenon, Antibody to ribonucleoprotein

Introduction

Raynaud's phenomenon (RP) is defined by the triple-phase sequence of blanching, cyanosis and erythema occurring spontaneously or in response to cold, physical or emotional stress[1]. Raynaud's disease is diagnosed in patients with no underlying structural vascular disease to explain the clinical findings. But, RP occurs in 90% of children with diffuse cutaneous systemic sclerosis, and other diseases including systemic lupus erythematosis (SLE), dermatomyositis, juvenile rheumatoid arthritis, and nonconnective tissue disease[1]. RP is much more common in the fingers, but can be observed in the toes and occasionally the ears, tip of the nose, lips, or tongue[1].

Mixed connective tissue diseases (MCTD), one of the underlying causes of RP, was initially described by Sharp and colleagues in 1972[2]. The syndrome includes the clinical features of rheumatoid arthritis, scleroderma, SLE, and dermatomyositis in conjunction with high titers of antibodies to extractable nuclear antigen (ENA), especially anti-ribonucleoprotein (anti-RNP) antibody[3]. Antibodies to ENAs include anti-Sm, anti-Ro/SS-A, anti-La/SS-B and anti-RNP antibodies[4]. Anti-RNP antibodies are found in low titers in children with SLE, but in high titers they are associated with mixed connective tissue disease[4]. Most cases of MCTD have been reported in adults. MCTD has been reported to have a frequency of 0.3%, in the U.S Pediatric Rheumatology Database[5]. Here we report the case of a rare pediatric patient with MCTD in a 7-year-old girl presenting initially with RP.

Received : 4 March 2008, Revised : 8 April 2008, Accepted : 20 June 2008
Address for correspondence : Young Ok Kim, M.D.
Department of Pediatrics, Chonnam National University Medical School
8 Hak-Dong, Dong-Gu, Gwangju 501-757, Korea
Tel : +82.62-220-6646, Fax : +82.62-222-6103
E-mail : ik052@unitel.co.kr

Case report

A seven-year-old girl was transferred to Chonnam National University Hospital due to painful cold sensations and reversible color changes in the fingers. She had complained of these symptoms when writing or when exposed to cold; in addition, these symptoms sometimes occurred in the feet. The onset of symptoms was 3 months before the visit. There was no family history of similar symptoms or of autoimmune disease.

On physical examination, the patient had swollen hands and ulceration of the tip of the right index finger (Fig. 1). The provocation test for the symptoms with writing and exposure to cold demonstrated RP appearing as a symmetric, triphasic (white → blue → red) progression that involved all of the fingers with well defined borders not extending beyond the wrist (Fig. 2). The patient complained of numbness,

Fig. 1. Ulceration on the tip of the right index finger before provocation testing for the Raynaud's phenomenon.

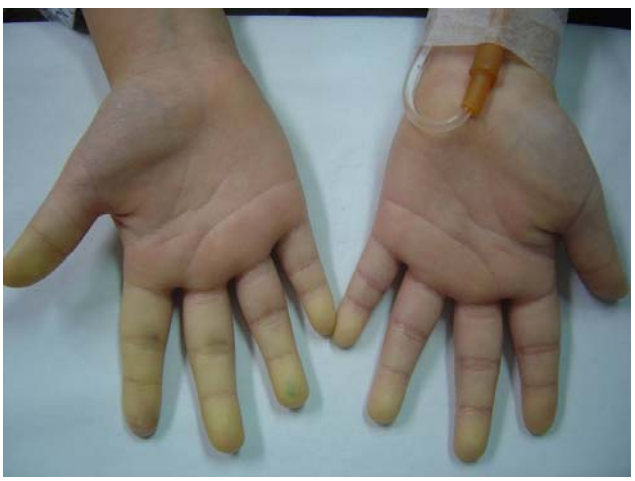

Fig. 2. Raynauds phenomenon, change in color from blue to white in both digits, after the stress provocation test.

paresthesia and pain during the provocation test.

The laboratory studies included a complete blood cell count, serum chemistry (e.g. serum total protein and albumin, electrolytes, liver, and kidney function, muscle enzymes and acute phase reactants) and urine analysis. All of the results were normal except for the lactate dehydrogenase (elevated to 831 U/L) and erythrocyte sedimentation rate (elevated to 61 mm/hr). Immunoglobulin and complement assays demonstrated elevated levels of IgG (3,060 mg/dL), IgE (821.0 IU/mL), C4 (57.50 mg/dL), and CH 50 (60.6 U/mL). However, there were normal levels of IgA, IgM and C3. Diagnostic laboratory profiles for rheumatological disease were performed. A speckled antinuclear antibody (ANA) pattern was observed with a very high titer of 1:320 and the level of anti-RNP antibody was elevated to 210.9 U/mL. However, the other autoantibodies were negative such as anti-Sm antibody, anti-double-stranded DNA antibody, anti-histon antibody, anti-SS-A (Ro) antibody, anti-SS-B (La) antibody, anti-centromere antibody, and anti-SCL 70 antibody. In addition, the RA factor, LE cell test and antiphospholipid antibody were also negative. The serology data and clinical characteristics supported the diagnosis of MCTD.

Even though the patient had no symptoms involving any specific organ, further studies due to the suspicion of MCTD included chest x-ray, chest computed tomography, electrocardiography, echocardiography, pulmonary function testing, esophagography, kidney ultrasonography, and thermography. The results of all of these studies showed non-specific findings except for the thermography, which revealed a significantly decreased surface temperature and an abnormal concentric temperature distribution on both hands and feet (Fig, 3).

To treat the Raynaud's phenomenon, slow release nifedipine was initially prescribed. But the symptoms did not improve with the nifedipine or with enalapril. Instead treatment with the steroid (deflazacort) significantly decreased the frequency and severity of the RP and healed the ulcer on the tip of the right index finger after a few months. In addition, the anti-RNP antibody decreased to 154.9 U/mL, although it was still positive. However, when tapering and maintaining the dose of deflazacort, alopecia and polyarthritis were newly observed. During follow up over the next two years, the patient continued to complain of intermittent RP and arthritis that was aggravated in the winter.

Discussion

In patients with MCTD, polyarthritis (93%) and RP (85%) are the most common manifestations at onset[3]. The arthritis is relatively painful and often associated with rheumatoid factor (RF) serosensitivity that is often present early in approximately two thirds of children[3]. In addition, antiphospholipid antibodies have been associated with RP and related disorders in adults[6], which are also frequently found in pediatric RP, whether primary or secondary[7]. The current case also presented with RP of the fingers, swollen hands and digital ulceration as the initial symptoms followed by the development of polyarthritis and alopecia even though initial antiphospholipid antibodies and RF were negative.

Other clinical manifestations and serology characteristics observed in MCTD are: peritendinous or subcutaneous nodules, sclerodermatous skin, SLE rash, dermatomyositis

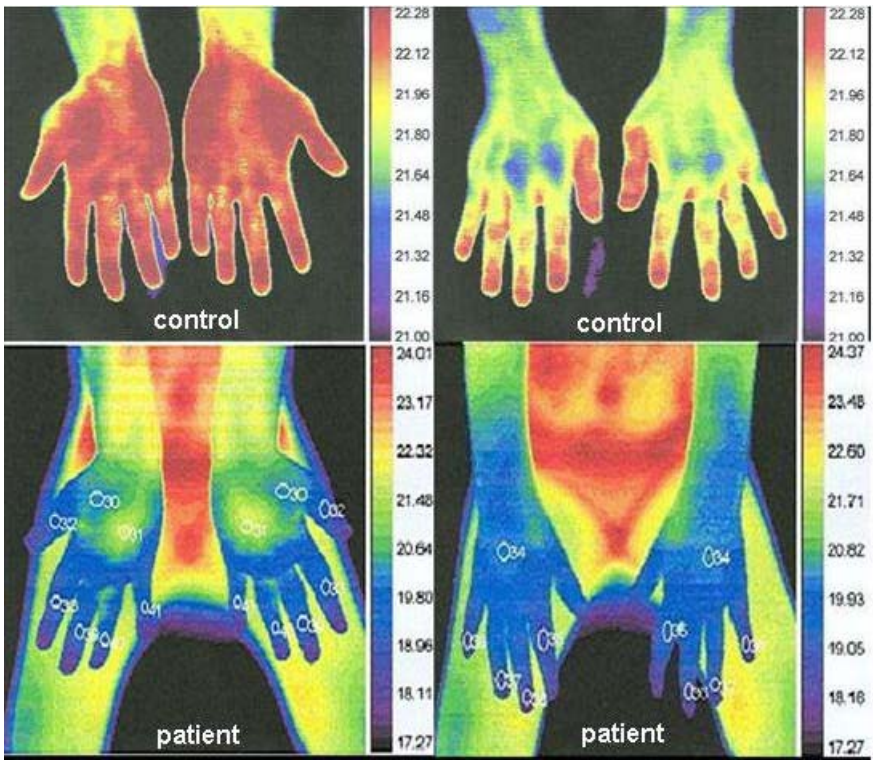

Fig. 3. Thermography revealing a significantly decreased surface temperature and an abnormal concentric temperature distribution on both hands in the patient (below) compared to that in the control (above).

Table 1. Classification and Diagnostic Criteria for Mixed Connective Tissue Disease

Sharp criteria[2, 11]	Major criteria 1. Severe myositis 2. Lung involvement: DLCO<70% and/or pulmonary hypertension and/or proliferative vascular lesions on biopsy 3. Raynaud phenomenon or oesophageal hypomotility 4. Swollen hands or sclerodactyly 5. Anti-ENA ≥1:10,000 with anti-RNP + and anti-Sm Minor criteria 1. Alopecia 2. Leukopenia <4,000 3. Anaemia 4. Pleuritis 5. Pericarditis 6. Arthritis 7. Trigeminal neuralgia 8. Malar rash 9. Thrombocytopenia 10. Mild myositis 11. History of swollen hands MCTD certain 4 major criteria, no anti-Sm, plus anti-U1-RNP>1:4,000 MCTD probable 3 major criteria and no anti-Sm; or 2 major criteria and 1 minor criterion; plus anti-U1-RNP>1:1,000

Table 1. Classification and Diagnostic Criteria for Mixed Connective Tissue Disease (Continued)

Alarcon-Segovia criteria[9, 11]	1. Serologic criteria anti-RNP at haemagglutination titer > 1:1,600 2. Clinical criteria a. swollen hands b. synovitis c. biologically or histologically proven myositis d. Raynauds phenomenon e. acrosclerosis with or without promimal systemic sclerosis MCTD if criterion 1 present and at least 3 clinical criteria (if a, d, and e are present, b or c are required as well)
Kasukawa criteria[10, 11]	1. Common symptoms a. Raynauds phenomenon b. Swollen fingers 2. Anti-RNP Ab 3. Symptoms A. of SLE: a. polyarthritis b. adenopathies c. malar rash d. pericarditis or pleuritis e. leucopenia or thrombocytopenia B. of SSc: a. sclerodactyly b. pulmonary fibrosis or restrictive change of lung or reduced DLCO c. hypomotility or oesophageal dialation C. of polymyositis a. muscle weakness b. elevated muscle enzymes c. myogenic signs on EMG MCTD if presence of at least 1 of the 2 common symptoms and Anti-RNP Ab + and presence of at least 1 sign of at least 2 of the following CTD: SLE, SSc, PM.
Kahn criteria[11]	1. Serologic criteria Presence of high titer anti-RNP corresponding to speckled ANA at titer ≥1:2000 2. Clinical criteria a. Raynauds phenomenon b. synovitis c. myositis d. swollen fingers MCTD if serologic criteria + and Raynauds phenomenon and at least 2 of the 3 following signs (synovitis, myositis and swollen fingers)

Abbreviations : DLCO, diffusing capacity; ENA, extractable nuclear antigen; U1-RNP, uridine-rich-ribonucleoprotein; SLE, systemic lupus erythematosis; SSc, systemic sclerosis; EMG, electromyography; CTD, connective tissue disease; PM, polymyositis; ANA, antinuclear antibody

rash, alopecia, fever, and sicca syndrome. In addition, abnormal esophageal motility presenting with the symptoms of dysphagia, pharyngeal globus sensation and heartburn, hepatomegaly, and splenomegaly have been reported. As well, cardiac disease, pericarditis, lung disease such as abnormal diffusion, restrictive disease, pulmonary hypertension and pleural effusion or pleuritis, muscle disease such as myositis, central nervous system disease, trigeminal neuropathy; and renal disease such as proteinuria and membranous nephropathy have also been observed. Furthermore, leucopenia, anemia, thrombocytopenia, anti-RNP positive and RF positive have been reported[3, 8, 9].

In cases with MCTD, very high titers of ANAs are usually present initially, often in a speckled pattern that reacts specifically with the RNAse-sensitive component of ENA, especially RNP[3]. MCTD is distinctive from other connective tissue diseases in its immune response to RNP. The titers of anti-RNP antibody are generally very high, usually higher than in patients with SLE[3, 8].

MCTD can be diagnosed based on the clinical and serologic findings. There are some criteria suggested for the diagnosis of MCTD in adults[2, 10, 11]. However, currently there are no standard criteria approved by the American College of Rheumatology (ACR) for adults or children. Nonetheless, several sets of diagnostic criteria for MCTD have been reported[2, 3, 10-12] (Table 1). Amigues et al[13] evaluated four sets of criteria proposed to be used for the diagnosis of MCTD: the criteria of Sharp, Alarcon-Segovia, Kasukawa, and Kahn. The criteria proposed by Alarcon-Segovia were the best for identifying patients with MCTD, with 62.5% sensitivity and 86.2% specificity.

There is no specific treatment for MCTD. Low-dose glucocorticoids, nonsteroidal anti-inflammatory drugs, hydroxychloroquine, or a combination of these medications is available for the treatment of children. Some have advocated the use of cytotoxic drugs such as cyclophosphamide and methotrexate[3]. The first step of treatment for RP is avoidance of precipitating circumstances such as cold or emotional stress. Then vasodilator agents can be prescribed such as calcium channel blockers, angiotensin converting enzyme inhibitors, prostaglandin E1, prostaglandin I1, reserpine, methyldopa, ketanserin, and griseofulvin[1]. In the current case, slow releasing nifedipine and enalapril had no effect on the RP symptoms but deflazacort resulted in improvement of the digital ulcer and a decrease in the frequency and severity of RP even though the effects of steroid treatment for RP have been reported not so good[8].

The long-term outcomes of children with MCTD vary and are unpredictable because of the paucity of information available and the short follow-up period in children. Sharp et al described MCTD as a relatively benign syndrome[2] but recently there have been debates about the outcome of MCTD[8, 14, 15]. Some of the controversial issues are these: 1) MCTD is not always benign or steroid responsive; 2) it may be transition to a classic connective tissue disease such as SLE, systemic sclerosis or rheumatoid arthritis; 3) there is a lack of specificity of anti-RNP antibody for MCTD; 4) there is no demonstrated role for anti-RNP antibody in the pathogenesis of MCTD[8]. Due to the complexity of potential organ involvement such as heart, kidney, lung, and central nervous system, in patients with MCTD, early identification and appropriate treatment can improve disease outcome[14, 15].

In summary, this report illustrates a rare case of childhood MCTD in a 7-year-old girl presenting initially with RP, swollen hands, mild sclerodactyly with ulceration of the tip of the right index finger followed by alopecia and polyarthritis during follow-up on steroid treatment.

한 글 요 약

레이노드 증후군으로 초기 발현된 복합 교원성 질환 1례

전남대학교 의과대학 소아과학교실

김수영 · 최영석 · 김영옥 · 우영종

복합 교원성 질환은 류마티스 관절염, 경피증, 전신성 홍반성 낭창, 다발성 근염의 다양한 임상양상을 나타내면서 혈청학적 검사에서 항 ENA 항체를 갖는 질환이다. 성인에서 1972년 25례의 복합 교원성 질환의 첫 보고 이래 국내에서 성인에서 발생한 복합 교원성 질환에 대한 몇몇 보고가 있었지만, 소아에서는 복합 교원성 질환의 보고가 드물다. 7세 여아가 내원 3개월 전부터 시작된 양 손가락에, 글쓰기 및 한랭노출에 의해 유발되는, 가역적인 색깔 변화와 차가움을 주소로 내원하였다. 신체 검사에서 양측 손가락들의 부종 및 오른쪽 집게손가락 끝에 궤양이 관찰되었다. 혈청학적 검사에서 다른 교원성 질환의 증거 없이 높은 역가의 ANA와 항 ENA 항체 중 항 RNP 항체가 고역가로 검출되었다. Raynaud 현상과 궤양에 대해 slow releasing nifedipin을 사용하였으나 호전 보이지 않아 스테로이드를 투약 하였고, 이후 궤양은 치유 되었으며, Raynaud 현상의 빈도도 현저히 감소하였다. 그러나 steroid를 점차 감량하는 동안 탈모 및 관절염 증상이 새로 발현되었으며, 현재 겨울에 악화되는 Raynaud 증상과 관절염으로 추적 관찰 중이다. 이에 본 저자들은 Raynaud 현상으로 발현되고 추적 동안에 탈모와 관절염이 나타난 복합 교원성 질환의 드문 소아 증례를 보고하는 바이다.

References

1) Francesco Z, James TC. Systemic sclerodermas and related disorders. In: James TC, Ross EP, Ronald ML, Carol B. Textbook of pediatric rhematology. 5th ed. Philadelphia : WB Saunders Co, 2005:447-61.
2) Sharp GC, Irvin WS, Tan EM, Gould RG, Holman HR. Mixed connective tissue disease-an apparently distinct rheumatic disease syndrome associated with a specific antibody to an extractable nuclear antigen (ENA). Am J

Med 1972;52:148-59.
3) James TC, Ross EPL. Overlap syndromes. In: James TC, Ross EP, Ronald ML, Carol B. Textbook of pediatric rhematology. 5th ed. Philadelphia : WB Saunders Co, 2005: 482-9.
4) Bowyer S, Roettcher P. Pediatric rheumatology clinic populations in the United States: results of a 3 year survey. Pediatric Rheumatology Database Research Group. J Rheumatol 1996;23:1968-74.
5) Ross EP, Ronald ML. Systemic lupus erythematosus. In: James TC, Ross EP, Ronald ML, Carol B. Textbook of pediatric rhematology. 5th ed. Philadelphia: WB Saunders Co, 2005: 370-1.
6) Vayssairat M, Abuaf N, Baudot N, Deschamps A, Gaitz JP. Abnormal IgG cardiolipin antibody titers in patients with Raynaud's phenomenon and/or related disorders: prevalence and clinical significance. J Am Acad dermatol 1998;38: 555-8.
7) Niqrovic PA, Fuhlbriqqe RC, Sundel RP. Raynaud's phenomenon in children: a retrospective review of 123 patients. Pediatrics 2003;111:715-21.
8) Peter J. Madison. Mixed connective tissue disease: overlap syndromes. Baillière's Clinical Rheumatology 2000;14:111-24.
9) Song CY, Cho S, Kim KM, Kim WY, Park YH, Oh JE, et al. A case presentation of renal involvement in MCTD. Korean J Med 2005;68:457-462.
10) Alarcon-Segovia D, Villareal M. Classification and diagnostic criteria for mixed connective tissue disease. In: Kasukawa R, Sharp GC, eds. Mixed connective tissue disease and anti-nuclear antibodies. Amsterdam: Excerpta Medica 1987:33-40.
11) Kasukawa R, Tojo T, Miyawaki S. Preliminary diagnostic criteria for classification of mixed connective tissue disease. In: Kasukawa R, Sharp GC, eds. Mixed connective tissue disease and anti-nuclear antibodies. Amsterdam: Excerpta Medica, 1987:41-8.
12) Wadhwa S. Deep vein thrombosis and haemolytic anaemia in a case of overlap syndrome. JIACM 2000;5:62-7.
13) Amigues JM, Cantagrel A, Abbal M, Mazieres B. Comparative study of 4 diagnosis criteria sets for mixed connective tissue disease in patients with anti-RNP antibodies. Autoimmunity Group of the Hospitals of Toulouse. J Rheumatol 1996;23:2055-62.
14) Yang YH, Tsai MJ, Lin SC, Lin MT, Chiang BL. Childhood mixed connective tissue disease. J Formos Med Assoc 2000;99:158-61.
15) Pope JE. Other manifestations of mixed connective tissue disease. Rheum Dis Clin North Am 2005;31:519-33.