A Case of Mixed Connective Tissue Disease Associated with Graves' Disease

Mikst Konnektif Doku Hastalığı ve Graves Hastalığı Birlikteliği: Bir Olgu Sunumu

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Abstract

A 23-year-old housewife admitted to hospital complained swelling, pain and skin color changes in both hands, and generalized arthralgia and myalgia. She had a butterfly malar rash, puffy hands, arthritis affecting the right second and third proximal interphalangeal and left knee joints. Anti-nuclear antibody was positive, anti-ribosomal nuclear protein antibody titer was found to be increased, C-reactive protein and erythrocyte sedimentation rate were slightly higher. Mixed connective tissue disease was diagnosed on the basis of the findings of synovitis, Raynaud's phenomenon and positive anti-ribosomal nuclear protein antibody and the patient was administered on a combination of oral prednisolone and methotrexate. After one year, a significant increase in the serum free T3 and free T4 and a suppression in thyroid stimulating hormone levels were noted. Both anti-microsomal and anti-thyroglobulin antibodies were also found to be increased. Thyroid scintigraphy with Tc-99 pertecnatat revealed a diffuse uptake pattern. The patient was diagnosed with Graves' disease and treated with anthythyroid drugs for 6 months and then radioactive iodine-131 ablation.

In conclusion, here we report a case with mixed connective tissue disease associated with Graves' disease which is an uncommon data in literature. *(Rheumatism 2008; 23: 100-2)*

Key words: Graves' disease, mixed connective tissue disease

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Özet

23 yaşında ev hanımı olan hasta her iki elde şişlik, ağrı, renk değişikliği, jeneralize artralji ve miyalji şikayetleri ile polikliniğimize başvurdu. Hastada kelebek raş, her iki el sırtında şişlik, sağ el 2. ve 3. proksimal interfalangeal eklemde ve sol diz ekleminde artrit vardı. Antinükleer antikor pozitifti, antiribozomal nükleer protein antikor titresi artmıştı. C reaktif protein ve eritrosit sedimentasyon hızı hafif yükselmişti. Sinovit, Raynaud fenomeni ve anti-ribonükleer protein pozitifliği göz önüne alınarak mikst konnektif doku hastalığı tanısı kondu ve hastaya oral prednisolon ve methotrexate tedavisi başlandı. Bir sene sonra serum serbest T3 ve serbest T4 değerlerinde yükselme ve tiroid stimulan hormon seviyelerinde düşüş tespit edildi. Antimikrozomal ve antitiroglobulin antikorları yüksek saptandı. Tc-99 ile yapılan sintigrafide diffüz tutulum mevcuttu. Bu bulgularla hastaya Graves hastalığı tanısı konarak propiltiyourasil ve propranolol tedavisi başlandı ve 6. ayda radyoaktif iyot ile ablasyon yapıldı.

Bu makalede, mikst konnektif doku hastalığı ile birlikte Graves hastalığı olan bir olgu rapor edilmiş ve bu konu ile ilgili literatür gözden geçirilmiştir. *(Rheumatism 2008; 23: 100-2)*

Anahtar sözcükler: Graves hastalığı, mikst konnektif doku hastalığı

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Introduction

Mixed Connective Tissue Disease (MCTD) is an overlap syndrome combining features of systemic lupus erythematosus (SLE), systemic sclerosis and polymyositis, together with anti-ribosomal nuclear protein antibody (U1-RNP) positivity. There are serological and clinical diagnostic criteria for MCTD. The serologic criterion is the presence of antibodies to U1-RNP and the clinical criteria including edema of the hands, synovitis, myositis, Raynaud's phenomenon and acrosclerosis. The diagnosis of MCTD requires the serologic and three clinical criteria. When edema, Raynaud's phenomenon and acrosclerosis are combined, four clinical criteria are required (1).

Graves' disease (GD) is an autoimmune thyroid disease which is characterized by hyperthyroidism with or without diffuse goiter, ophthalmopathy, pretibial mixedema and thyroid acropathy (2, 3). It has been reported that autoimmune thyroid diseases such as Hashimoto's thyroiditis (HT) and GD may overlap with other autoimmune systemic and organ-specific disorders including pernicious anemia, myasthenia gravis, Addison's disease, immune

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thrombocytopenia, vitiligo and type 1 diabetes mellitus. However, there is relatively less information regarding the overlap of autoimmune thyroid diseases such as HT or GD with MCTD (4-6). Here we report a case with MCTD associated with GD.

Case

A 23-year-old housewife admitted to the Department of Physical Medicine and Rehabilitation of our University Hospital with complaints of swelling and pain in both hands as well as generalized arthralgia and myalgia persisting for one year. She also described changes in skin color of her hands (pale to bluish and reddish) when exposed to cold. She had no relevant family history. On her physical examination, she had malar rash in the appearance of butterfly. In addition, she had soft tissue swelling in the form of puffy hands. Arthritis of the right second and third proximal interphalangeal and left knee joints were also observed. Her liver and spleen were not palpable. No other systemic examination finding was obtained. On laboratory analysis; anti-nuclear antibody (ANA) was positive, anti-RNP titer was found increased. Both C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) were slightly high. Cryoglobuline was negative, cryofibrinogen was positive and complement 3 (C3) was increased. The patient was diagnosed with MCTD on the basis of the presence of anti-RNP and three clinical criteria including edema of the hands, synovitis, Raynaud's phenomenon. At her initial presentation, the thyroid functions including free T3 (fT3), free T4 (fT4) and thyroid-stimulating hormone (TSH) were normal. Afterwards, she was started on a combination of oral prednisolone and methotrexate for the management of MCTD. On the latter follow-ups there was marked decrease in ESR and CRP values (ESR, from 65 to 23 and CRP, from 36 to 3.06). Thyroid function tests were still normal on these follow-ups. One year after her initial presentation, the patient's complaints of sweating, tremor and tachycardia started. Thyroid function tests were measured and found as follows: Serum fT3, fT4 and TSH levels were 7.56 pg/mL (2.3-4.2 pg/mL), 2.15 ng/dL (0.89-1.8 ng/dL) and 0.005 mIU/L (0.35-5.5 mIU/L) respectively. Both anti-microsomal (ATPO) and anti-thyroglobulin (ATrg) antibodies were found to be increased to 600 U/ml (0-60 U/ml) and 491 U/ml (0-120 U/ml) respectively. A thyroid scanning with Tc-99 pertecnatate revealed a diffuse uptake pattern. Ophthalmopathy, thyroid acropachy and pretibial myxedema were not found. HLA A2, A3, B7, B35, DRB1, 04, 08 and DRB4 was found in the serological analysis. Based on these findings, Graves' disease was diagnosed and combination of propilthyrouracil and propranolol treatment was started. But the patient showed a bad treatment compliance. Therefore Radioactive Iodine (I131) treatment was given in July 2006. Four months later, the patient became euthyroid and clinically stable. ESR and CRP levels were decreased to normal levels.

Discussion

Connective tissue disease patients are reported to be at high risk for the development of thyroid dysfunction (7). MCTD, systemic sclerosis and Sjögren's syndrome patients can be associated with auto-immune thyroid diseases such as Hashimoto's thyroiditis and, to a lesser extent Graves' disease. But, there is not enough study reporting the connection between auto-immune thyroid disease and MCTD (4). Hämeenkorpi et al. (8) reported 4 patients with thyroid disease and/or thyroid antibodies among 25 patients with MCTD syndrome a study done by Sharp and colleagues. Biro et al. (4) found that only 4 of 159 MCTD patients had had Graves' disease. Arnaout et al. (7) studied 170 connective tissue disease patients (11 had MCTD) and found 3 cases with thyrotoxic Graves' disease. In addition, none of these 11 MCTD patients had positive ATPO. Authors concluded that, although the clinical diagnosis of thyroid disease was uncommon in patients with connective tissue disease, abnormal thyroid function test results were frequently found in these patients. Hämeenkorpi et al. (8) investigated 22 MCTD patients out of 140 patients with connective tissue diseases. Authors reported that five patients with MCTD had elevated titers of ATrg and/or ATPO antibodies together with normal thyroid function test results, three patients had hypothyroidism, and none of the patients had hyperthyroidism. The presented case had both abnormal thyroid function tests with positive ATPO, ATrg and clinically overt hyperthyroidism. HLA B8, DR3 and/or DR4 are seen more common among patients with connective tissue diseases or autoimmune thyroid disease (7, 8). In our patient HLA-DRB1 04,08 allele of HLA DR4 serologic antigens were positive consistent with the mentioned reports.

It has been also reported that, MCTD is usually associated with hypothyroidism, whereas patients with systemic vasculities have higher frequency of hyperthyroxinemia (7). This patient was presented with the clinical findings of MCTD and then she had hyperthyroidism with the signs of GD after 12 months. The later finding is quite interesting, because we had a chance to see the development of GD during 12 months period. Clinical overt ophthalmopathy was not seen in this case. We may suggest for this finding that immunosuppressive therapy for MCTD can influence the development of ophthalmopathy. However, thyroid ophthalmopathy can develop later, after the first attack of GD.

In conclusion, this case has some interesting aspects; firstly, MCTD associated with GD is relatively rare, and secondly, the time period of development of GD has been observed. Physicians who care MCTD patients should be aware of this coexistence and investigate the thyroid pathology.

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