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CASE REPORT

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A rare case of systemic sclerosis complicated with multiple autoimmune diseases (Sjögren's syndrome, Graves' disease, and primary biliary cirrhosis)

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Abstract We report the case of a 54-year-old woman with systemic sclerosis and Sjögren's syndrome, followed by a simultaneous onset of Graves' disease and primary biliary cirrhosis. Eight years after the patient was diagnosed with systemic sclerosis and secondary Sjögren's syndrome, she complained of thirst and lower extremity muscle weakness. Initially, these symptoms were thought to be due to her original diseases, but laboratory data revealed thyroid dysfunction as well as liver dysfunction, and further tests confirmed the diagnoses of Graves' disease and primary biliary cirrhosis. The patient was treated with thiamazole and ursodeoxycholic acid. Following treatment, her symptoms were relieved, and laboratory data improved. Although a combination of these diseases is rare, it is important to keep in mind that various autoimmune diseases can occur simultaneously, and early detection and therapy are important.

Key words Autoimmune diseases · Graves' disease (GD) · Primary biliary cirrhosis (PBC) · Sjögren's syndrome (SS) · Systemic sclerosis (SSc)

Introduction

An autoimmune disease is often accompanied by another autoimmune disease. The association between autoimmune thyroid disease, an organ-specific condition, and connective tissue disease, a systemic condition, is quite common, although the exact mechanism behind this is unclear. There have been very few reports concerning the association between Graves' disease and other systemic autoimmune diseases. We describe a case of Graves' disease and primary biliary cirrhosis occurring with systemic sclerosis and Sjögren's syndrome.

Case report

A 54-year-old Japanese woman presented with symptoms of joint pain and Raynaud's phenomenon. Her past history was unremarkable. Her family history included an older sister with Hashimoto's thyroiditis and a younger sister with Graves' disease.

A physical examination revealed sclerodactylia, i.e., scleroderma of the arms and body. Her serum was positive for antinuclear antibody (discrete speckled) and anticentromere antibody. Along with a positive skin biopsy, the patient was diagnosed as having limited cutaneous-type systemic sclerosis. At the same time, she showed symptoms of keratoconjunctivitis sicca and xerostomia, a positive Schirmer test and gum test, and findings of focal lymphocytic infiltration with minor salivary gland biopsy; anti-SS-A and SS-B antibodies were negative. The patient was diagnosed as having secondary Sjögren's syndrome. No other complications were observed, and she was prescribed d-penicillamine. The patient was followed as an outpatient for the next 8 years, with no significant disease progression.

In November 2002, a laboratory test showed mild liver enzyme elevations, and the following month she complained of thirst and lower extremity muscle weakness. Initially, it was thought that these symptoms were part of the clinical manifestations of her systemic sclerosis and Sjögren's syndrome. However, a physical examination revealed a diffused goiter, and neurological examinations for the muscle strength of the quadriceps femoris, hamstrings, and gluteus maximus muscle were all 3/5. A urinalysis was normal. Her erythrocyte sedimentation rate was increased, although C-reactive protein remained negative. Abnormal

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Table 1. Laboratory findings

ESR	30 mm/h
Hematology	
WBC	4620/μl
Neu	54.8%
Eo	1.1%
Lym	37.2%
RBC	470 × 10^4/μl
Hb	12.8 g/dl
Plt	13.6 × 10^4/μl
Blood chemisstry	
TP	7.5 g/dl
T-bil	1.1 mg/dl
AST	62 IU/l
ALT	53 IU/l
LDH	207 IU/l
ALP	1079 IU/l
γGTP	78 IU/l
CK	40 IU
BUN	11.7 mg/dl
Cre	0.4 mg/dl
Na	142 mEq/l
K	4.2 mEq/l
Cl	103 mEq/l
Serology	
CRP	0.14 mg/dl
IgG	1785 mg/dl
IgA	231 mg/dl
IgM	305 mg/dl
ANA	×1280 (DS)
Anti-SS-A antibody	(–)
Anti-SS-B antibody	(–)
Anti-Scl-70 antibody	(–)
Anti-U1-RNP antibody	(–)
Anti-centromere antibody	175 Index
Anti-mitochondria M2 antibody	×20
Thyroid	
TSH	0.02 μIU/ml
fT3	26.0 pg/ml
fT4	5.94 ng/dl
TSAb	1689%
TRAb	71%
Thyroglobulin	89 ng/ml
Anti-thyroglobulin antibody	5.8 IU/ml
Anti-TPO antibody	0.3< IU/ml

TP, total protein; T-bil, total bilirubin; AST, aspartate aminotransferase; ALT, alanine aminotransferase; LDH, lactate dehydrogenase; ALP, alkaline phosphatase; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; ANA, antinuclear antibody; TSH, thyroid stimulating hormone; fT3, free T3; fT4, free T4; TSAb, thyroid stimulating antibody; TRAb, anti-TSH receptor antibody; Anti-TPO antibody, antithyroid peroxidase antibody

laboratory findings included elevated liver enzymes, elevated immunoglobulin M (IgM), high antinuclear antibody titer, positive anticentromere antibody, and a positive antimitochondria M2 antibody (Table 1). Thyroid function revealed decreased thyroid-stimulating hormone (TSH), elevated fT4, positive thyroid stimulation antibody, anti-TSH receptor antibody, antithyroglobulin antibody, and antithyroid peroxidase antibody. Viral hepatitis antibody and antigen titers were all negative, and abdominal ultrasonography revealed only a small liver cyst.

From these laboratory findings, the patient was diagnosed as having Graves' disease. Although a liver biopsy was not performed, elevated liver enzymes, increased IgM, and a positive antimitochondria M2 antibody also suggested primary biliary cirrhosis.

The patient was treated with ursodeoxycholic acid, thiamazole, and a beta-blocker. Her symptoms subsided, and her laboratory findings improved.

Discussion

One autoimmune disease is often associated with another, suggesting the influence of a common immunological dysfunction in the pathogenesis of these diseases. This also applies to autoimmune thyroid diseases and their association with other systemic autoimmune disorders. Although autoimmune thyroid diseases, such as Hashimoto's thyroiditis and Graves' disease, have been reported with various systemic autoimmune diseases, reports of Hashimoto's thyroiditis are more common. Hashimoto's thyroiditis and/or elevated antithyroid antibody titers have been reported in rheumatoid arthritis, systemic lupus erythematosus, Sjögren's syndrome, polymyalgia rheumatica, temporal arthritis, relapsing polychondritis, systemic sclerosis, and primary biliary cirrhosis. In contrast, reports of complications with Graves' disease are scarce. We present a rare case of systemic sclerosis (SSc) complicated by the multiple autoimmune diseases of Sjögren's syndrome (SS), Graves' disease (GD), and primary biliary cirrhosis (PBC).

Systemic sclerosis (SSc), which is characterized by inflammatory, fibrotic, and degenerative changes in multiple organ systems, is often associated with a broad spectrum of autoimmune thyroid diseases. Most of these studies report cases of SSc associated with Hashimoto's thyroiditis rather than with GD. The prevalence rates of hypothyroidism and SSc range from 23% to 65%, while the presence of antithyroid antibody among SSc patients ranges from 18% to 52%.[1–4] Gordon et al.[3] found an increased frequency of antithyroid antibodies, hypothyroidism, and euthyroid sick syndrome, and their pathological examination of the thyroid in patients with SSc revealed a high frequency of thyroid fibrosis and thyroiditis at autopsy. In contrast, the occurrence with hyperthyroidism, such as GD, is less common and reports are rare (Table 2). The reason for this rarity compared with Hashimoto's thyroiditis is unknown, and it may be due to the fact that there are more cases of Hashimoto's thyroiditis among this sex and age group than of GD. However, there are suggestions of a common genetic predisposing factor for both GD and SSc. In the Caucasian population, *HLA-B8* and *HLA-DR3* can often be found among the two diseases.[13,14] There are no studies that are specifically targeted towards locating the genetic sites for patients with both SSc and autoimmune thyroid disease in the Japanese population. However, *HLA-DRB1*, *DQBI*, and *CTLA-4* are some of the prevalent genes involved with both diseases.[15–18] A review of our study and previous reports of GD and SSc reveal that women are prone to these diseases and that SSc is likely to be the initial disease. There seems to be no relation between the times of onset of the accompanying disease and the types of SSc.

Table 2. Systemic sclerosis associated with Graves' disease

Case	Age/sex	Type of SSc	Initial disease	Time until onset	Antibodies	Association with Sjögren's	Ref.
SSc + GD	45/f		SSc	3 years		None	5
SSc + GD	40/m		GD	1 year		None	6
SSc + GD	39/f	Limited	SSc	5 years	Microsomal Ab (+) Antithyroglobulin (−) Scl-70 (−)	None	7
SSc + GD	37/f	Diffused	SSc	5 years	Microsomal Ab (+) Antithyroglobulin (−)	None	7
SSc + GD + SS	53/f		SSc	13 years	Microsomal Ab (+)	Yes	7
SSc + GD + CH	57/f	Limited	SSc	1 month	Microsomal Ab(+) RNP (−)	ND	8
SSc + GD + PM	49/f		All		Microsomal Ab (+), ANA (+)	ND	9
SSc + GD + SS	62/f	Diffused	GD	5 years	Microsomal Ab (+) ANA (−), Scl-70 (−) Antithyroglobulin (−)	Yes	10
SSc + GD	59/m	Diffused	SSc	10 years	TRAb (+)	None	11
SSc + GD + DM + ITP	35/f	Limited	SSc + DM	10 years	Microsomal Ab (+) Antithyroglobulin (+) TBII (+) ANA (+), Scl-70 (+)	ND	12
SSc + SS + GD + PBC	54/f	Diffused	SSc + SS	8 years	Microsomal Ab (+) Antithyroglobulin (+) ANA (+), Scl-70 (−), RNP (−)	Yes	Present case

SSc, systemic sclerosis; GD, Graves' disease; CH, chronic hepatitis; SS, Sjögren's syndrome; ND, not done; PM, polymyositis; ANA, antinuclear antibody; DM, dermatomyositis; TRAb, anti-TSH receptor antibody; TBII, TSH-binding inhibition immunoglobulin; ITP, immune thrombocytopenic purpura; f, female; m, male

However, the small number of cases makes an accurate analysis difficult.

Primary biliary cirrhosis (PBC) is a chronic cholestatic liver disease that is frequently associated with other autoimmune diseases, including thyroid disorders, SSc, and SS. Thyroid disease is found in about 10%–15% of patients with PBC, and Hashimoto's thyroiditis is the most common.[19] To our knowledge, there is only one report concerning a PBC and GD association.[20]

Sjögren's syndrome (SS) is often observed with thyroid diseases. There are several speculations as to why this occurs. Embryologically, salivary glands and thyroid arise from the same cell, and there may be a cross-immunity between these two glands.[21] Histopathologically, the lymphocytic infiltrates of lacrimal and salivary glands that are found in SS are similar to those of the thyroid gland in Hashimoto's thyroiditis.[22] The prevalence of Hashimoto's thyroiditis with primary SS varies from 10% to as high as 54%.[22,23] There is a high incidence of antibodies against thyroglobulin, thyroid peroxidase, and thyroid hormones in SS patients, indicating that subclinical autoimmune thyroid disease in SS is fairly common.[24,25] Twenty-five percent of patients with autoimmune thyroid disease have significant focal sialoadenitis, which suggests that subclinical SS frequently occurs in thyroid patients.[26] In contrast, hyperthyroidism with SS is rare; there are only four reports that describe hyperthyroidism and primary SS, and their prevalence rates are low, ranging from 3% to 12%.[27–30] An interesting point is that there are several reports of thyroid diseases, SS, and other autoimmune disorders which suggest that SS may be an immunological disorder linking autoimmune thyroid diseases and disorders such as SSc and PBC. One study showed that out of the 29 SSc patients who also had SS, 48.3% also had Hashimoto's thyroiditis.[21] Crowe et al.[19] showed that there was a statistically significant association between SS, PBC, and thyroid dysfunction compared with PBC and thyroid dysfunction alone.

Table 3. Common symptoms of Graves' disease and systemic sclerosis

General fatigue
Muscle weakness
Frequent defacation
Palpitation
Weight loss
Malabsorption
Dyspnea, chest pain, dyspnea on exertion
Scleroderma or scleroderma-like skin thickening
Skin pigmentation, vitiligo
Alopecia

The reasons why multiple disorders occur together are still widely discussed. In Caucasian patients, these diseases show a frequent association with *HLA-B8*, *DR3*, and/or *DR4* compared with the general population.[31,32] Another study showed prevalances of autoimmune thyroid diseases among patients with SS and their first- and second-degree relatives.[33] NKT cell counts are relatively low in patients with autoimmune diseases, and this may be involved in the development of multiple autoimmune diseases.[34] In animals, thymectomy alone produced multiorgan-specific autoimmune diseases, thus suggesting that some kind of common immunologic pathway exists.[35] Further studies involving the roles of T cells and genetic analysis are still needed to clarify the relation between autoimmune diseases.

The present case is a rare occurrence of SSc complicated by SS, and later by GD and PBC. Clinically, one must bear

in mind that there are similar clinical manifestations between these disorders, and this may lead to a delayed diagnosis of more life-threatening conditions. For example, it is essential to monitor the thyroid functions of SSc patients routinely (Table 3). Although prevalence rates differ and the mechanisms are only speculative, one must always be aware that multiple autoimmune diseases can occur simultaneously.

References

1. De Keyser L, Narihi DC, Furst DE, Huberman AK, Ross R, Clements J, et al. Thyroid dysfunction in a prospectively followed series of patients with progressive systemic sclerosis. J Endocrinol Invest 1990;13:161–9.
2. Kahl L, Medsger T, Klein I. Prospective evaluation of thyroid function in patients with systemic sclerosis (scleroderma). J Rheum 1986;13:103.
3. Gordon MB, Klein I, Dekker A, Rodnan GP, Medsger TA Jr. Thyroid disease in progressive systemic sclerosis: increased frequency of glandular fibrosis and hypothyroidism. Ann Intern Med 1981;95:431–5.
4. Kuchartz EJ. Thyroid disorders in patients with progressive systemic sclerosis: a review. Clin Rheumatol 1993;12:159–61.
5. Shoaleh-var M, Momtaz AH, Jamshidi C. Scleroderma and hyperthyroidism. JAMA 1976;235:752–3.
6. Ward JA, Mendeloff JD, Coberley JC. Hyperthyroidism followed by scleroderma. JAMA 1977;237:1123.
7. Nicholson D, White S, Lipson A, Jacobs RP, Borenstein DG. Progressive systemic sclerosis and Graves' disease. Arch Intern Med 1985;146:2350–2.
8. Yamada T, Iizuka K, Yuasa K, Saeki S, Abe T, Sakurai S, et al. A case of chronic hepatitis complicated with progressive systemic sclerosis and Graves' disease (in Japanese). Nippon Shokakibyo Gakkai Zasshi 1985;82:2850–4.
9. Hatakeyama M, Miyagi J, Takeda A, Masuyama J, Sumiya M, Gonda N, et al. A case of progressive systemic sclerosis complicated with polymyositis and Graves' disease (in Japanese). Ryumachi 1983;23:155–62.
10. Anzai H, Tajima S. Systemic scleroderma associated with Graves' disease. J Dermatol 1996;23:869–8.
11. Ghayad E, Thome A, Haddad F, Haddad C, Choueiry R. Scleroderma with anomalies of the thyroid function: 7 cases (in French). Ann Med Interne (Paris) 1997;148:307–10.
12. Kamei N, Yamane K, Yamashita Y, Nakanishi S, Watanabe H, Fujikawa R, et al. Anti-Ku antibody-positive scleroderma-dermatomyositis overlap syndrome developing Graves' disease and immune thrombocytopenic purpura. Internal Medicine 2002; 41:1199–203.
13. Trence DL, Morley JE, Handwerger BS. Polyglandular autoimmune syndromes. Am J Med 1984;77:107–16.
14. Kallenberg CG, van der Voort-Beelen JM, D'Amaro J, The TH. Increased frequency of B8/DR3 in scleroderma and association of haplotype with impaired cellular immune response. Clin Exp Immunol 1981;43:478–85.
15. Terauchi M, Yanagawa T, Ishikawa N, Ito K, Fukazawa T, Maruyama H, et al. Interactions of *HLA-DRB4* and *CTLA-4* genes influence thyroid function in Hashimoto's thyroiditis in Japanese population. J Endocrinol Invest 2003;26:1208–12.
16. Hiratani H, Akamizu T. Association study on candidate loci of susceptible genes of autoimmune thyroid diseases in a Japanese population (in Japanese). Rinsho Byori 2001;491151–6.
17. Kuwana M, Inoko H, Kameda H, Nojima T, Sato S, Nakamura K, et al. Association of human leukocyte antigen class II genes with autoantibody profiles, but not with disease susceptibility in Japanese patients with systemic sclerosis. Intern Med 1999;38:336–44.
18. Takeuchi F, Kawasugi K, Nabeta H, Mori M, Tanimoto K. Association of *CTLA-4* with systemic sclerosis in Japanese patients. Clin Exp Rheumatol 2002;20:823–8.
19. Crowe JP, Christensen E, Butler J, Wheeler P, Doniach D, Keenan J, et al. Primary biliary cirrhosis: the prevalence of hypothyroidism and its relationship to thyroid autoantibodies and sicca syndrome. Gastroenterology 1980;78:1437–41.
20. Takigawa H, Kowa H, Kitayama M, Doi S, Araga S, Nakashima K. Manifestation of primary biliary cirrhosis and Basedow's disease caused by exposure to carbon monoxide in a patient with HTLV-1-associated myelopathy (in Japanese). Rinsho Shinkeigaku 2000; 40:344–9.
21. Hashikabe M, Miyazaki T, Hara N, Yamakage A, Yamazaki S. Systemic sclerosis associated with Hashimoto disease (in Japanese). Jpn J Dermatol 2002;112:233–8.
22. Karsh J, Pavilidis N, Weintraub BD, Moustsopoulos HM. Thyroid disease in Sjögren's syndrome. Arthritis Rheum 1980;23: 1326–9.
23. Foster H, Fay A, Charles KP, Walker D, Griffiths I. Thyroid disease and other autoimmune phenomena in a family study of primary Sjögren's syndrome. Br J Rheumatol 1993;32:36–40.
24. Trimarchi F, Benvenga S, Costante G, Barbera C, Melluso R, Marcocci C, et al. Identification and characterization of circulating thyroid hormone autoantibodies in thyroid diseases, in autoimmune non-thyroid illnesses and lymphoreticular system disorders. J Endocrinol Invest 1983;6:203–9.
25. Sakata S, Nakamura S, Miura K. Autoantibodies against thyroid hormones or iodothyronine. Implications in diagnosis, thyroid function, treatment, and pathogenesis. Ann Intern Med 1985;103: 579–89.
26. Wemeau JL, Dessaint JP, Leonardeli J, Rouget JP, Racadot A, Linquette M. Hypothyroidism and the Gougerot–Sjögren syndrome (in French). Ann Med Interne (Paris) 1983;134:288.
27. Kelly CA, Foster H, Pal B, Griffiths I. What is the incidence of thyroid disease in primary Sjögren's syndrome? Br J Rheumatol 1990;29:36.
28. Perez-EB, Kraus A, Lopez G, Cifuentes M, Alarcon-Segovia D. Autoimmune thyroid disease in primary Sjögren's syndrome. Am J Med 1995;99:480–4.
29. Punzi L, Ostuni PA, Betterle C, DeSandre P, Botsois C, Gambari PF. Thyroid gland disorders in primary Sjögren's syndrome. Rev Rheum Engl Ed 1996;63:809–14.
30. Ramos-Casals M, Garcia-Carrasco M, Cervera R, Gaya J, Halperin I, Ubieto I, et al. Thyroid disease in primary Sjögren's syndrome. Medicine 2000;79:103–8.
31. Renertsen JL, Klippel JH, Johnson AH, Steinberg AD, Ducker JL, Mann DL. B-lymphocyte alloantigens associated with systemic lupus erythematosus. N Engl J Med 1987;299:515–8.
32. Dahlberg PA, Holmlund G, Karlsson FA, Safwenberg J. HLA-A, -B, -C, and –DR antigens in patients with Graves' disease and their correlation with signs and clinical course. Acta Endocrinol 1981; 97:42–7.
33. Foster H, Fay A, Charles KP, Walker D, Griffiths I. Thyroid disease and other autoimmune phenomena in a family study of primary Sjögren's syndrome. Br J Rheumatol 1993;32:36–40.
34. Dunne J, Lynch S, O'Farrelly C, Todryk S, Hegarty JE, Feighery C, et al. Selective expansion and partial activation of human NK cells and NK receptor-positive T cells by IL-2 and IL-15. J Immunol 2001;167:3129–38.
35. Bonomo A, Kehn PJ, Payer E, Rizzo L, Cheever AW, Shevach EM. Pathogenesis of post-thymectomy autoimmunity. Role of syngenic MLR-reactive T cells. J Immunol 1995;15:6602–11.