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CASE REPORT

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A case of amyloidosis secondary to rheumatoid arthritis complicated with Graves' ophthalmopathy

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Abstract We report the case of a 73-year-old woman who suffered from amyloidosis secondary to rheumatoid arthritis (RA) complicated with Graves' ophthalmopathy. She had goiter, diplopia, and exophthalmos with polyarthralgia. We diagnosed Graves' ophthalmopathy with thyroid-stimulating hormone (TSH)-receptor antibodies (TBII and TSAb). The amyloid deposit was detected in her stomach. The complication of Graves' ophthalmopathy in amyloidosis secondary to RA has rarely been reported.

Key words Amyloidosis · Graves' ophthalmopathy · Rheumatoid arthritis (RA)

Introduction

Amyloidosis is a serious complication of rheumatoid arthritis (RA) and suggests a poor prognosis. In systemic amyloidosis, amyloid infiltration is found in multiple organs. It has been reported that the incidence of an association of RA and Hashimoto thyroiditis is high, whereas that of RA and Graves' disease is rare.[1] Furthermore, it is very rare for Graves' disease to be complicated with amyloidosis secondary to RA. Only one previous case of amyloidosis secondary to RA complicated by Graves' disease has been reported.[2] In this case report, we present a patient with a goiter due to Graves' disease who showed high titers of anti-thyroid-stimulating hormone (TSH) receptor autoantibodies in amyloidosis secondary to RA.

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Case report

A 73-year-old woman was admitted to our hospital in December 1999 with arthralgia of the left knee joint and double vision. She had been diagnosed with goiter in about 1980. She reported having experienced symptoms of arthralgia and morning stiffness since 1991. She was diagnosed with RA in 1992, and was treated with loxoprofen sodium alone. This treatment did not ease her symptoms; in fact, she felt increased arthralgia and morning stiffness. She visited our hospital in August 1997, and was prescribed 2.5 mg prednisolone (PSL) per day. In March 1998, she began to experience watery diarrhea and weight loss (−6 kg in 2 months). Upon admission to our hospital, a diagnosis of amyloidosis was made, based on findings from endoscopic gastrointestinal biopsies. Her course of oral medicine was stopped, and her diarrhea was controlled by intravenous hyperalimentation (IVH). Because her renal function had worsened due to the secondary amyloidosis (blood urea nitrogen (BUN) 25–43 mg/dl, creatinine (Cre) 1.2–1.5 mg/dl, creatinine clearance (Ccre) 19–28.5 ml/min), she began taking 15 mg PSL per day and 1.25 mg methotrexate (MTX) per week to regulate her RA. Her arthralgia and the swelling of the left knee joint decreased, and the inflammatory markers improved. The patient's goiter, palpitations, and elevated levels of thyroid hormones (free T3 4.2 pg/ml, free T4 2.6 ng/dl) suggested hyperthyroidism. Furthermore, her thyrotropin-binding inhibitory immunoglobulin (TBII) activity and thyroid-stimulating antibody (TSAb) were 70% and 175%, respectively. She stopped taking MTX and reduced her dose of PSL subsequent to experiencing stomatitis in April 1999. Her arthralgia and the swelling of the left knee joint became severe, and her renal functions worsened, resulting in her admission to our hospital. At the time of admission, she also had diplopia and exophthalmos, and was diagnosed with Graves' ophthalmopathy.

On admission, the patient's height was 152 cm and her body weight was 43 kg. Her body temperature was 36.5°C, pulse rate 72/min, blood pressure 136–76 mmHg, and respiration rate 14/min. She had exophthalmos with proptosis

Table 1. Laboratory data on admission

WBC	6400/mm^3
RBC	434 × 104/mm^3
Hb	11.7 g/dl
Plt	22.8 × 104/mm^3
TP	5.2 g/dl
Alb	2.4 g/dl
BUN	31 mg/dl
Cre	2.1 mg/dl
Ccre	20.8 ml/min
AST	15 IU/l
ALT	10 IU/l
LDH	133 IU/l
ALP	291 IU/l
CK	14 IU/l
Tcho	121 mg/dl
ESR	68 mm/h
CRP	5.76 mg/dl
RF	85.1 IU/ml
SAA	20.1 μg/ml
IgG	672 mg/dl
IgA	140 mg/dl
IgM	120 mg/dl
FreeT3	4.3 pg/ml
FreeT4	1.6 ng/ml
TSH	<0.05 μU/ml
Thyroid test	25 600×
Microsome test	25 600×
TBII activity	62.6% (<±10%)
TSAb	2122% (<180%)
U-Prot	2.3 g/day
U-RBC	(−)
HLA type	HLA–A24, A26, B54, B62, CW1, CW3 HLA–DR4, DR15, DQ1, DQ4

WBC, white blood cells; RBC, red blood cells; Hb, hemoglobin; Plt, platelets; TP, total protein; Alb, albumin; BVN, blood urea nitrogen; Cre, creatinine; Ccre, creatinine clearance; AST, aspartate aminotransferase; ALT, alanine aminotransferase; LDH, lactic dehydrogenase; ALP, alkaline leukocyte phosphatase; CK, creatine kinase; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; RF, rheumatoid factor; SAA, serum amyloid A; TSH, thyroid-stimulating hormone; TBII, thyrotropin-binding inhibitory immunoglobulin; TSAb, thyroid-stimulating antibody; Tcho, total cholesterol

(19 mm in the left eye and 18 mm in the right eye, according to Hertel measurements). Her left eyeball deviated to the left lateral side. Her field of vision was restricted, and diplopia appeared when she glanced to the right. Her thyroid was enlarged to twice the normal size, and her left knee joint was swollen and red. Her lower extremities were edematous. No neurological abnormalities were seen except that muscle weakness in her grasping power (right 15 kg, left 7 kg) was noted.

Laboratory examination revealed the following results (Table 1): urinalysis, proteinuria (2.3 g/day); erythrocyte sedimentation rate, 68 mm/h; white blood cell count, 6400/mm^3; red blood cell count, 434 × 10^4/mm^3; hemoglobin, 11.7 g/dl; platelet count, 22.8 × 10^4/mm^3; total protein, 5.2 g/dl; albumin, 2.4 g/dl; BUN, 31 mg/dl; Cre, 2.1 mg/dl; CCre, 20.8 ml/min; aspartate aminotransferase (AST), 15 IU/l; alanine aminotransferase (ALT), 10 IU/l; lactic dehydrogenase (LDH), 133 IU/l; creatine kinase (CK), 14 IU/l; alkaline leukocyte phosphatase (ALP), 291 IU/l; C-reactive protein, 5.76 mg/dl; rheumatoid factor, 85.1 IU/ml; serum amyloid A (SAA), 20.1 μg/ml. IgG, IgA, and IgM were 672, 140, and 120 mg/dl, respectively. Thyroid hormone tests revealed free T3 at 4.3 pg/ml, free T4 at 1.6 ng/ml, and TSH at less than 0.05 μU/ml. Both the thyroid test and the microsome test were 25 600×. TBII activity and TSAb activity were 62.6% (<±10%) and 2122% (<180%), respectively. HLA type included A24, A26, B54, B62, CW1, CW3, DR4, DR15, DQ1, and DQ4. Tumor necrosis factor-α (TNF-α) was 34 pg/ml. Interleukin-1β (IL-1β), IL-4, IL-6, IL-10, and interferon-γ (IFN-γ) were not detected. X-rays of the left knee joint taken upon admission to our hospital in December 1999 revealed destruction of the joint surface and narrowing of the joint space. A thyroid echogram showed mild swelling of both lobes. The internal echo was iso- or hypoechoic with hyperechoic spots. A magnetic resonance imaging (MRI) of the orbital lesion showed swelling of the eye muscles (Fig. 1). Histopathological studies revealed amyloid deposition in the patient's stomach (Fig. 2). The amyloid deposition was stained by Congo red, and was noted especially around vessels; the stains were decreased through treatment with potassium permanganate. These data suggested that this deposition was the AA amyloid type. No amyloid deposition was detected in the specimens of the thyroid provided by aspiration biopsy.

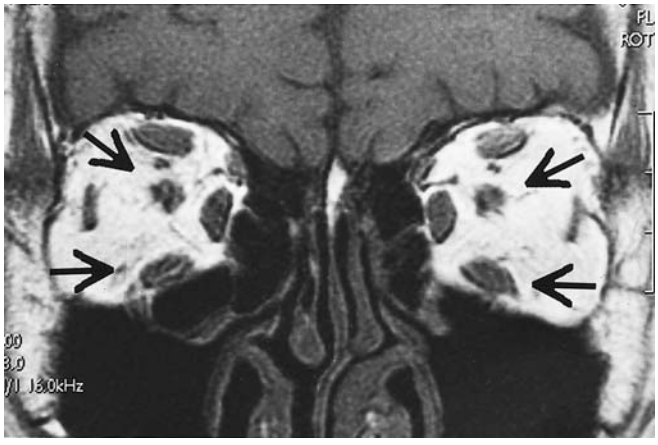

Fig. 1. MRI of the patient's orbital lesion taken on December 27, 1999. Swelling of the extraocular muscles was detected

We performed pulse methylprednisolone therapy in order to treat the Graves' ophthalmopathy (Fig. 3). The patient's arthralgia and the swelling in the joint disappeared. The restriction of the visual field and double vision also improved, although there was no change in the swelling of the eye muscles. Exophthalmos improved by 15 mm on both sides, according to Hertel measurements. Thyroid function remained within normal limits. TBII activity decreased from 62.60% to 21.40%, although TSAb activity was essentially stable at the previous level (2085%) 1 month after the administration of pulse methylprednisolone therapy.

Discussion

This RA patient, who suffered from amyloidosis complicated by Graves' ophthalmopathy, was diagnosed with

euthyroid Graves' disease based on clinical symptoms (goiter and exophthalmos) and the existence of anti-TSH receptor autoantibodies (TBII and TSAb). We suspected that amyloidosis might also be present in her thyroid because the echogram of her thyroid revealed a heterogeneous echo with a mixture of hyperechoic lesions, although we were unable to detect any amyloid deposition in her thyroid. Aspiration biopsy specimens revealed inflammatory cell infiltration and thyroid follicular epithelial cells. Amyloid deposition was detected in specimens from the patient's stomach. It has been reported that the coincidence of RA, amyloidosis, and Hashimoto thyroiditis is high. However, amyloidosis secondary to RA complicated by Graves' disease has previously been reported only once.[2]

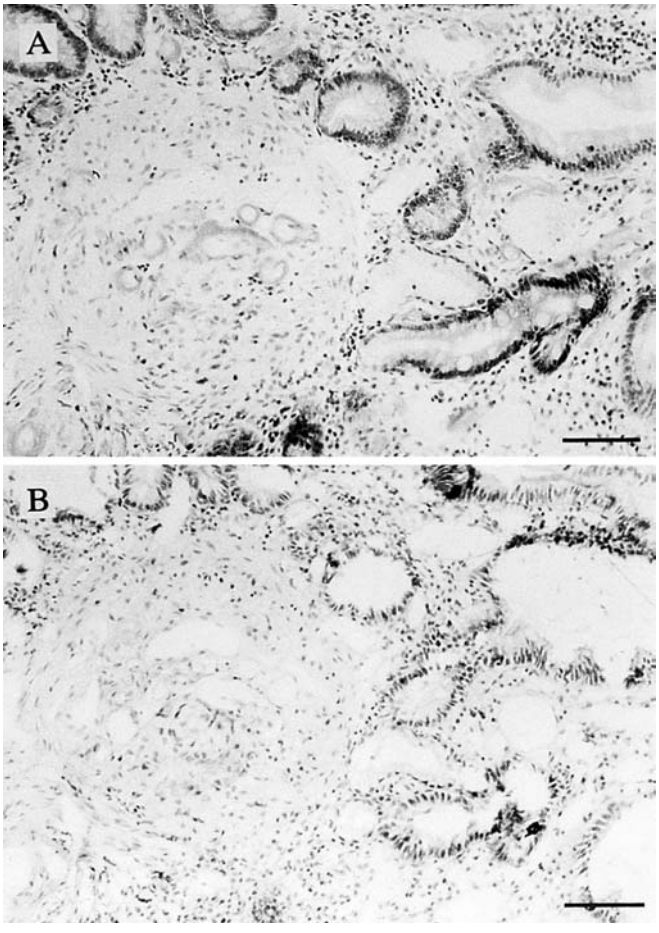

Fig. 2. Congo red staining of the stomach. **A** An amyloid substance was shown around the vessels (colored stain ×100). *Bar* 100 μm. **B** The staining decreased after treatment with potassium permanganate. *Bar* 100 μm

It is known that the putative orbital autoantigen, TSH receptor, can play a pivotal role within the orbit in Graves' ophthalmopathy. Various autoantibodies, including anti-TSH receptor antibody, are detected at high rates in patients with RA. Ruggeri et al.[3] demonstrated that thyroid hormone autoantibodies in RA were as prevalent as those in Graves' disease. Kirkegaard and Bliddal[4] reported 17 cases (68%) with TSAb and two cases (8%) with TBII out of 25 patients with RA. Although the frequency of anti-TSH receptor antibodies in amyloidosis has not yet been established, it is believed that anti-TSH receptor antibodies are detected at high rates.

Why is Graves' disease rarely complicated with RA? The relation between Graves' disease and RA cannot be explained by anti-TSH receptor alone. We considered the possibility of a rare complication between Graves' disease and RA.

First, although TSAb and TBII are detected at high rates in patients with RA, the effects of these antibodies may be different in Graves' disease. Recently, Noh et al.[5] reported that TBII was related to hyperthyroidism and TSAb was related to Graves' ophthalmopathy in patients with Graves' disease. When our patient was diagnosed with hyperthyroidism in 1998, her TBII was elevated to 70%. She was treated with pulse methylprednisolone therapy for Graves' ophthalmopathy (see Fig. 3). After the treatment, her thyroid hormone levels decreased with the decline of TBII. On the other hand, both exophthalmos and double vision were found in our patient on admission, and her TSAb had

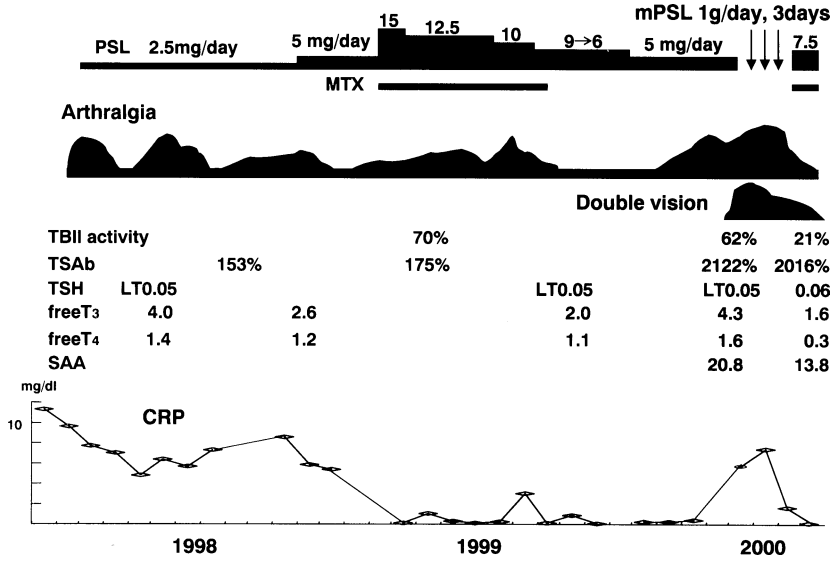

Fig. 3. The clinical course of this case. *PSL*, prednisolone; *mPSL*, methylprednisolone; *MTX*, methotrexate; *SAA*, serum amyloid protein A; *TBII activity*, thyrotropin-binding inhibitory immunoglobulin activity; *TSAb*, thyroid-stimulating antibody; *free T3/T4*, free thyroxine; *TSH*, thyroid-stimulating hormone; *CRP*, C-reactive protein

increased to a level ten times higher than that before the onset of ophthalmopathy. Her TSAb remained at a high level even after pulse methylprednisolone therapy. MRI did not reveal any changes in extraocular muscle enlargement, although the patient's ocular symptoms decreased, which might have been due to the decline of retroorbital fatty tissue edema. It was suggested that TSAb might have played an important role in eye muscle enlargement in this patient.

Second, cytokine expressions in Graves' disease and RA might be different. Many cytokines which might impact the expression of TSH receptor were found to be elevated in patients with Graves' ophthalmopathy,[6] and it is controversial which is predominant locally in the orbit. Valyasevi et al.[7] suggested that TNF-α, IFN-γ, and transforming growth factor-β might act within the orbit in Graves' ophthalmopathy to alter expression of the putative orbital autoantigen TSH receptor. On the other hand, Many et al.[8] suggested from animal model experiments that an autoimmune response of IL-4 or IL-10 to the TSH receptor is required for the development of Graves' ophthalmopathy. In our patient, we found an increased serum TNF-α concentration. It was presumed that TNF-α might induce autoantibodies to TSH receptor. TSH receptor antibodies, which are detected in many RA patients, are apparently related to the clinical course of Graves' ophthalmopathy. However, it is very rare for Graves' disease to be complicated with RA. It was suggested that anti-TSH receptor antibodies might be insufficient, independently, to induce the coincidence of Graves' ophthalmopathy and RA.

Third, the differences in HLA antigens might be related to a rare complication of Graves' disease in RA. It is well known that HLA–DR4 is associated with RA. HLA–DR4 has been reported to be significantly associated with the presence of rheumatoid factor and more severe radiographic changes.[9] A high prevalence of HLA–DR4 was found in patients with RA complicated by amyloidosis as compared with control blood.[10] The frequency of HLA–DR4 was also found to be increased in patients with Hashimoto thyroiditis.[11] RA, amyloidosis, and Hashimoto thyroiditis are genetically associated. However, Graves' disease has not been associated with HLA–DR4; the susceptible HLA antigens of Graves' disease are HLA–DR3 and HLA–B8.[12,13] The coexistence of certain genetic associations might also be required for the complication of Graves' ophthalmopathy in RA. The HLA type might be an important factor in the complication of Graves' disease and RA. Ohtsuka and Nakamura[14] reported that the severity of Graves' ophthalmopathy was associated with HLA–DQ1. Given that our patient had not only HLA–DR4 but also HLA–DQ1, the HLA–DQ1 antigen might have influenced the progression of Graves' ophthalmopathy in this case. In the future, genetic analyses of these diseases will be conducted, and their association with these various antigens will be clearer.

We have presented a case report of Graves' ophthalmopathy associated with amyloidosis secondary to RA. The anti-TSH receptor antibodies, which are relatively high in RA, may have contributed to the development and progression of Graves' ophthalmopathy in this case, although it is necessary to accumulate further cases to define the association characteristic of these diseases.

References

1. Shiroky JB, Cohen M, Ballachey ML, Neville C. Thyroid dysfunction in rheumatoid arthritis: a controlled prospective survey. Ann Rheum Dis 1993;52:454–6.
2. Kimura H, Yamashita S, Ashizawa K, Yokoyama N, Nagataki S. Thyroid dysfunction in patients with amyloid goitre. Clin Endocrinol (Oxford) 1997;46:769–74.
3. Ruggeri RM, Galletti M, Mandolfino MG, Aragona P, Bartolone S, Giorgianni G, et al. Thyroid hormone autoantibodies in primary Sjögren's syndrome and rheumatoid arthritis are more prevalent than in autoimmune thyroid disease, and becoming progressively more frequent in these diseases. J Endocrinol Invest 2002;25:447–54.
4. Kirkegaard C, Bliddal BH. Thyroid-stimulating antibodies in rheumatoid arthritis: an in vitro phenomenon. J Endocrinol Invest 1987;10:495–8.
5. Noh JY, Hamada N, Inoue Y, Abe Y, Ito K. Thyroid-stimulating antibody is related to Graves' ophthalmopathy, but thyrotropin-binding inhibitor immunoglobulin is related to hyperthyroidism in patients with Graves' disease. Thyroid 2000;10:809–13.
6. Wakelkamp IMMJ, Gerding MN, van der Meer JWC, Prummel MF, Wiersinga WM. Both Th1- and Th2-derived cytokines in serum are elevated in Graves' ophthalmopathy. Clin Exp Immunol 2000;121:453–7.
7. Valyasevi RW, Jyonouchi SC, Dutton CM, Munsakul N, Bahn RS. Effect of tumor necrosis factor-alpha, interferon-gamma, and transforming growth factor-beta on adipogenesis and expression of thyrotropin receptor in human orbital preadipocyte fibroblasts. J Clin Endocrinol Metab 2001;86:903–8.
8. Many MC, Costagliola S, Detrait M, Dnenef F, Vassart G, Ludgate MC. Development of an animal model of autoimmune thyroid eye disease. J Immunol 1999;162:4966–74.
9. Olsen NJ, Callahan LF, Brooks RH, Nance EP, Kaye JJ, Stastny P, et al. Associations of HLA–DR4 with rheumatoid factor and radiographic severity in rheumatoid arthritis. Am J Med 1988;84:257–64.
10. Maury CP, Teppo AM, Wafin F, Wegelius O, Friman C, Koshkimies S, et al. Class-specific rheumatoid factors, DR antigens, and amyloidosis in patients with rheumatoid arthritis. Ann Rheum Dis 1988;47:546–52.
11. Farid N, Thompson C. HLA and autoimmune endocrine disease 1985. Mol Biol Med 1986;3:85–97.
12. 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 (Copenhagen) 1981;97:42–7.
13. Azuma Y, Sakurami T, Ueno Y, Ohishi M, Saji H, Terasaki PI, et al. HLA–DR antigens in Japanese with Hashimoto's thyroiditis and Graves' disease. Endocrinol Jpn 1982;29:423–7.
14. Ohtsuka K, Nakamura Y. Human leukocyte antigens associated with hyperthyroid Graves ophthalmopathy in Japanese patients. Am J Ophthalmol 1998;126:805–10.