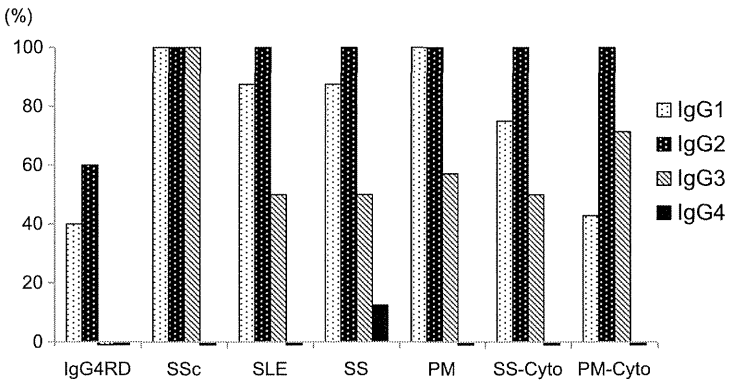

Fig. 2 Positivity of each ANA subclass in IgG4-RD and systemic autoimmune diseases. Cyto: positivity of each subclass of anti-cytoplasmic antibody was also calculated for patients with Sjögren's syndrome and polymyositis

Table 2 ANA profiles of patients with systemic autoimmune diseases

Case	ANA	Specific autoantibodies	IgG4[a]	IgG[a]
SLE 1[b]	Spe 320	dsDNA, ssDNA, U1-RNP, Sm	21.3	1830
SLE 2	Homo + Spe 320	dsDNA, ssDNA, SS-A	11	826
SLE 3	Spe 1280	dsDNA, ssDNA, Sm, Ribosome	20	2043
SLE 4	Spe 640	ssDNA, U1-RNP, Sm, SS-A, SS-B	8.3	829
SLE 5	Homo + Spe 1280	dsDNA, ssDNA, U1-RNP, Sm, SS-A, SS-B	7	556
SLE 6	Homo + Spe 160	ssDNA	48.6	1938
SLE 7	Spe 320	dsDNA, SS-A	19.6	1186
SLE 8	Spe 5120	dsDNA, ssDNA, U1-RNP, Sm, SS-A	7	908
SSc 1	Discrete spe 1280	Centromere	7	1177
SSc 2[b]	Discrete spe 1280, Spe 160, Cyto 80	Centromere, SS-A	21.2	1772
SSc 3	Spe 1280	Scl-70, U1-RNP, SS-A	25.5	2147
SSc 4	Discrete spe 1280	Centromere, Scl-70, U1-RNP	12.4	1108
SS 1	Spe 320	SS-A, SS-B	33.4	2974
SS 2	Spe 160	SS-A, SS-B	16.5	1765
SS 3	Spe 80	SS-A, SS-B	74	1370
SS 4[c]	Spe 640	SS-A	228	1721
SS 5	Spe 40, Cyto 80	SS-A	38	2133
SS 6	Spe 160	SS-A, SS-B	14.5	2340
SS 7	Spe 160	SS-A, SS-B	9.5	1882
SS 8[b]	Spe + Nucleolar 80, Cyto 40	SS-A	20.1	1678
PM 1	Spe + Nucleolar 640	Ku	53.5	1668
PM 2[b]	Spe 320, Cyto 40	ssDNA, U1-RNP, Sm, SS-A	12.9	1132
PM 3	Spe 40, Cyto 160	PL-7	15	717
PM 4	Spe 320	U1-RNP, Sm	5	282
PM 5	Spe 1280	Ku, SS-A, SS-B	<3	823
PM 6	Spe 40, Cyto 80	SRP	18.4	1365
PM 7	Homo + Spe 160	Not detected	19	2051

[a]mg/dL in serum. [b]Shown in Fig. 3. [c]Shown in Fig. 4
ANA: anti-nuclear antibody; Cyto: cytoplasmic; Discrete spe: discrete speckled; Homo: homogeneous; RNP: ribonucleoprotein; Spe: speckled; SRP: signal recognition particle

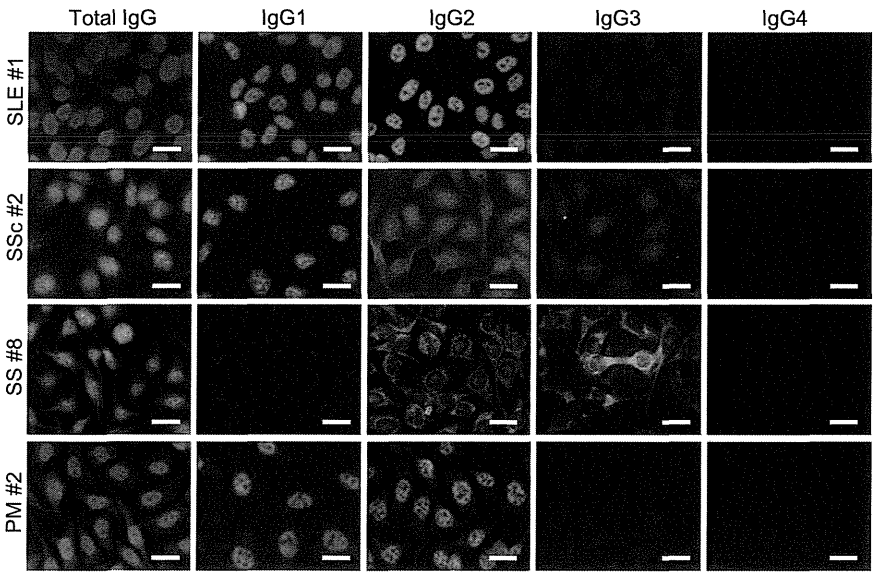

Fig. 3 Subclass-based ANA test for systemic autoimmune diseases showing immunofluorescence microscopy for each typical case, including systemic lupus erythematosus (SLE #1), systemic sclerosis (SSc #2), Sjögren's syndrome (SS #8) and polymyositis (PM #2) showed variation in ANA patterns among IgG subclasses. In SSc #2, total IgG showed Discrete spe + Speckled + Cyto, while IgG1 showed Discrete spe + Speckled, IgG2 showed Discrete spe + Speckled + Cyto, IgG3 showed Discrete spe + Cyto, and IgG4 showed negative. In SS #8, total IgG showed Speckled + Nucleolar + Cyto, while IgG1 and IgG2 showed Speckled + Cyto, IgG3 showed Nucleolar + Cyto, and IgG4 showed negative. Bar = 20 μm Discrete spe: discrete speckled, Cyto: cytoplasmic

the second antibodies are different. In past studies, IgG2-type ANA was also detected at moderate levels, whereas IgG4-type ANA was constantly negative or at low levels. In our study, IgG4-type ANA was also hardly detected.

Autoimmune pancreatitis (AIP) is an organ-specific disorder seen in IgG4-RD. Various autoantibodies, such as anti-lactoferrin [5] and anti-carbonic anhydrase II [6] antibodies, are seen in AIP. Asada et al. found anti-pancreatic secretory trypsin inhibitor (PSTI) antibody in AIP, and showed that the titers of anti-PSTI antibody moved in parallel with serum IgG4 levels [16]. IgG4 levels change in parallel with IgG4-RD disease activity, as reported in many studies, including our previous study [17]. Asada et al. thought that anti-PSTI might be an important factor in the pathophysiology. However, immunoblotting of subclasses with anti-IgG1 or anti-IgG4 as second antibodies showed the subclass was not IgG4 but IgG1. Possibly, IgG4-type autoantibodies are difficult to produce in IgG4-RD patients.

However, some autoimmune diseases reportedly show IgG4-type autoantibodies. Rock et al. reported that IgG4

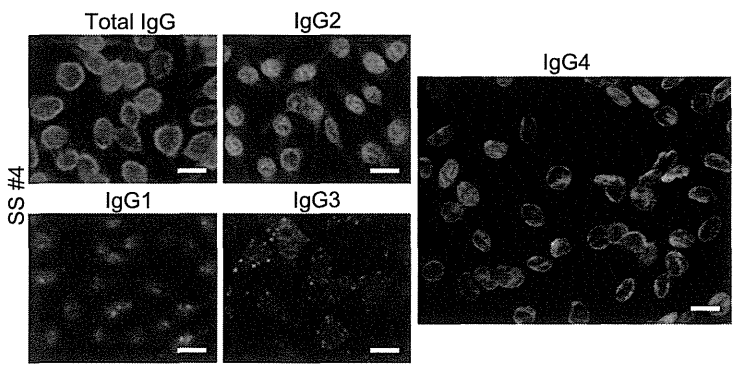

Fig. 4 Subclass-based ANA test of a patient with Sjögren's syndrome (SS #4) showing IgG4-type ANA. ANA patterns differed among IgG subclasses. Total IgG showed Speckled, while IgG2 showed Speckled + Cyto, IgG1 and IgG3 showed Nucleolar + Cyto (with atypical cytoplasmic spots), and IgG4 showed Peripheral. Bar = 20 μm. Cyto: cytoplasmic

was the most common (100 %) of anti-desmoglein (Dsg)-1 antibodies detected in sera of patients with pemphigus foliaceus, and showed the pathogenicity of IgG4-type anti-Dsg-1 antibody using Balb/c mice [18]. Anti-Dsg-3 antibody in pemphigus vulgaris was also IgG4-predominant [19]. Beck et al. showed by immunoblotting that anti-phospholipase A_2 receptor (PLA_2R) antibody in idiopathic membranous nephropathy mainly consisted of IgG4 [20]. IgG4 is reportedly predominant in anti-neutrophil cytoplasmic antibody (ANCA). C-ANCA (IIF), proteinase-3 (PR3)-ANCA (ELISA), and myeloperoxidase (MPO)-ANCA (ELISA) in granulomatosis with polyangiitis (GPA) [21], and MPO-ANCA (ELISA) in propylthiouracil-induced vasculitis [22] were IgG1/4-dominant. Others similarly reported that IgG4 made up most C-ANCA (IIF) and PR3-ANCA (ELISA) in vasculitides [23, 24]. Engelmann et al. reported that anti-cyclic citrullinated peptide (CCP) antibody was IgG1/4-dominant in RA [25]. However, IgG4 in vasculitides and RA might not be pathophysiologically important. In functional analyses of ANCA, IgG1 and IgG3 PR3-ANCA can stimulate neutrophils [26], whereas IgG4 PR3-ANCA was only weakly stimulatory to neutrophils [27]. In RA patients who had HLA-DR4-shared epitope, Engelmann et al. found IgG3 anti-CCP antibody to be predominant, and considered that IgG3-type antibody might be more important in the pathophysiology of RA [28]. As IgG4 has poor ability to activate complements and antibody-dependent cellular cytotoxicity [29–32], IgG4 is unlikely to take part in mechanisms of tissue damage in autoimmune diseases.

Interestingly, there seem to be pathogenic and non-functional IgG4-type autoantibodies. IgG4-type ANCA is considered less pathogenic, compared to other subclass ANCA in ANCA-associated vasculitis [26, 27]. The affinities between IgG4-type and other subclass ANCA should be equal, but the abilities of complement activation are different, so that the role of IgG4-type ANCA can be less significant than that of other subclass ANCA. On the other hand, IgG4 anti-PLA_2R antibody has high affinity and is considered pathogenic in idiopathic membranous nephropathy [20]. Why IgG4 anti-PLA_2R antibody can exert pathogenicity without ability of complement activation may be because the pathogenicity is brought by the destruction of electrical barriers of glomerular basement membrane.

Taken together, IgG4 usage rates differ among autoantibodies and among diseases. IgG4 is associated with anti-Dsg-1/3, anti-PLA_2R, anti-CCP antibodies, and ANCA, but not with anti-PTSI antibody in AIP or ANA in IgG4-RD and systemic autoimmune diseases (Table 3). This asymmetry implies that IgG4 has unknown but certain physiological or pathological functions. Further analyses are needed to know its role.

In the present study, we observed ANA patterns differed among IgG subclasses in some cases (Fig. 3, 4). When a case has several autoantibodies, the utilized subclasses differ by autoantigens. This can be explained by the hypothesis that each IgG subclass prefers to cover its own spectrum of antigens. The reason we hardly found IgG4 in ANA might be that IgG4 does not cover antigens that can be detected by the ANA test—i.e., nuclear antigens or related microbial antigens. Selective IgG2 subclass deficiency is often associated with bacterial infection by *Neisseria meningitidis* and *Streptococcus pneumoniae* [33, 34], so that IgG2 is considered to have a role in protection from these bacteria. The role of IgG4 has not been sufficiently understood. If IgG4 is related to some microorganism type, and if the microorganism antigens and autoantigens are similar, as with Dsg-1/3, PLA_2R, PR3, and citrullinated proteins, it would explain why IgG4-type antibody against those proteins was dominantly generated.

Our results imply that IgG4-RD is not an autoimmune disease, and that high levels of serum IgG4 in IgG4-RD are only nonspecific. Subclass-based ANA tests in this study covered both nuclear and cytoplasmic antigens in HEp-2 cells, and can screen a wide range of unmodified ubiquitous antigens. However, this analysis has limitations: modified antigens like citrullinated proteins and

Table 3 Summary of predominant subclasses in autoantibodies in IgG4-RD and autoimmune diseases

Diseases	Autoantibodies	Predominant subclass	IgG4 subclass	Reports
IgG4-RD	ANA	IgG2	Negative	Present study
IgG4-RD (AIP)	Anti-PSTI	IgG1	Negative	Asada [16]
SLE, SSc, SS, PM	ANA	IgG1/2/3	Seldom	Present study, Zouali [11], Eisenberg [12], Maran [13], Vazquez-abad [14]
GPA, Vasculitis	ANCA	IgG1, IgG4	Frequent	Brouwer [21], Mellbye [23], Liu [24], Gao [22]
RA	ACPA	IgG1, IgG4	Frequent	Engelmann [25]
PF, PV	Anti-Dsg-1/3	IgG4	Primary	Rock [18], Ding [19]
Idiopathic MN	Anti-PLA_2R	IgG4	Primary	Beck [20]

ACPA: anti-citrullinated protein antibody; AIP: autoimmune pancreatitis; ANA: anti-nuclear antibody; ANCA: anti-neutrophil cytoplasmic antibody; Dsg-1/3: desmoglein-1 and 3; GPA: granulomatosis with polyangiitis; MN: membranous nephropathy; PF: pemphigus foliaceus; PLA_2R: phospholipase A_2 receptor; PSTI: pancreatic secretory trypsin inhibitor; PV: pemphigus vulgaris; RA: rheumatoid arthritis

organ-specific antigens are not screened. The number of cases is limited in this study. There remains a possibility that unknown IgG4-type autoantibodies might be found in IgG4-RD. A further analysis is needed.

Conclusions

We found ANA in IgG4-RD patients are not IgG4-based despite high serum IgG4 levels. IgG4 was also hardly found in ANA in systemic autoimmune diseases. We also observed several patients in whom ANA patterns differed among IgG subclasses, probably due to difference in corresponding autoantigens. These findings imply that each IgG subclass tends to cover its own spectrum of antigens, and IgG4 is not apparently used to make ANA.

Abbreviations

ANA: Anti-nuclear antibody; ANCA: Anti-neutrophil cytoplasmic antibody; AIP: Autoimmune pancreatitis; CCP: Cyclic citrullinated peptides; dsDNA: Double-stranded deoxyribonucleic acid; Dsg: Desmoglein; ELISA: Enzyme-linked immunosorbent assay; GPA: Granulomatosis with polyangiitis; HLA: Human leukocyte antigen; IgG4-RD: Immunoglobulin G4-related disease; IIF: Indirect immunofluorescence; MPO: Myeloperoxidase; PLA_2R: Phospholipase A_2 receptor; PM: Polymyositis; PR3: Proteinase-3; PTSI: Pancreatic secretory trypsin inhibitor; RA: Rheumatoid arthritis; RNP: ribonucleoprotein; SLE: Systemic lupus erythematosus; SS: Sjögren's syndrome; SSc: Systemic sclerosis..

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

TM provided the idea of IgG4-subclass autoantibody in IgG4-RD. K. Kiyama and HY designed the study and collected the clinical data. K. Kiyama, HY, TK, and RN performed experiments and evaluations. DK gave significant suggestions and advice to the study. All the authors contributed to the composition of the manuscript.

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References

1. Masaki Y, Dong L, Kurose N, Kitagawa K, Morikawa Y, Yamamoto M, et al. Proposal for a new clinical entity, IgG4-positive multiorgan lymphoproliferative syndrome: analysis of 64 cases of IgG4-related disorders. Ann Rheum Dis. 2009;68(8):1310–5.
2. Okazaki K, Uchida K, Miyoshi H, Ikeura T, Takaoka M, Nishio A. Recent concepts of autoimmune pancreatitis and IgG4-related disease. Clin Rev Allergy Immunol. 2011;41(2):126–38.
3. Umehara H, Okazaki K, Masaki Y, Kawano M, Yamamoto M, Saeki T, et al. A novel clinical entity, IgG4-related disease (IgG4RD): general concept and details. Mod Rheumatol. 2012;22(1):1–14.
4. Umehara H, Okazaki K, Masaki Y, Kawano M, Yamamoto M, Saeki T, et al. Comprehensive diagnostic criteria for IgG4-related disease (IgG4-RD), 2011. Mod Rheumatol. 2012;22(1):21–30.
5. Okazaki K, Uchida K, Ohana M, Nakase H, Uose S, Inai M, et al. Autoimmune-related pancreatitis is associated with autoantibodies and a Th1/Th2-type cellular immune response. Gastroenterology. 2000;118(3):573–81.
6. Nishi H, Tojo A, Onozato ML, Jimbo R, Nangaku M, Uozaki H, et al. Anti-carbonic anhydrase II antibody in autoimmune pancreatitis and tubulointerstitial nephritis. Nephrol Dial Transplant. 2007;22(4):1273–5.
7. Hochberg MC. Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum. 1997;40(9):1725.
8. Fujibayashi T, Sugai S, Miyasaka N, Hayashi Y, K T: Revised Japanese criteria for Sjögren's syndrome (1999): availability and validity. Mod Rheumatol 2004(14):425–434.
9. Preliminary criteria for the classification of systemic sclerosis (scleroderma). Subcommittee for scleroderma criteria of the American Rheumatism Association Diagnostic and Therapeutic Criteria Committee. Arthritis Rheum 1980, 23(5):581–590.
10. Bohan A, Peter JB. Polymyositis and dermatomyositis (first of two parts). N Engl J Med. 1975;292(7):344–7.
11. Zouali M, Jefferis R, Eyquem A. IgG subclass distribution of autoantibodies to DNA and to nuclear ribonucleoproteins in autoimmune diseases. Immunology. 1984;51(3):595–600.
12. Eisenberg RA, Dyer K, Craven SY, Fuller CR, Yount WJ. Subclass restriction and polyclonality of the systemic lupus erythematosus marker antibody anti-Sm. J Clin Invest. 1985;75(4):1270–7.
13. Maran R, Dueymes M, Pennec YL, Casburn-Budd R, Shoenfeld Y, Youinou P. Predominance of IgG1 subclass of anti-Ro/SSA, but not anti-La/SSB antibodies in primary Sjogren's syndrome. J Autoimmun. 1993;6(3):379–87.
14. Vazquez-Abad D, Monteon V, Senecal JL, Walsh S, Rothfield N. Analysis of IgG subclasses of human antitopoisomerase I autoantibodies suggests chronic B cell stimulation. Clin Immunol Immunopathol. 1997;84(1):65–72.
15. Rigopoulou EI, Davies ET, Pares A, Zachou K, Liaskos C, Bogdanos DP, et al. Prevalence and clinical significance of isotype specific antinuclear antibodies in primary biliary cirrhosis. Gut. 2005;54(4):528–32.
16. Asada M, Nishio A, Uchida K, Kido M, Ueno S, Uza N, et al. Identification of a novel autoantibody against pancreatic secretory trypsin inhibitor in patients with autoimmune pancreatitis. Pancreas. 2006;33(1):20–6.
17. Kiyama K, Kawabata D, Hosono Y, Kitagori K, Yukawa N, Yoshifuji H, et al. Serum BAFF and APRIL levels in patients with IgG4-related disease and their clinical significance. Arthritis Res Ther. 2012;14(2):R86.
18. Rock B, Martins CR, Theofilopoulos AN, Balderas RS, Anhalt GJ, Labib RS, et al. The pathogenic effect of IgG4 autoantibodies in endemic pemphigus foliaceus (fogo selvagem). N Engl J Med. 1989;320(22):1463–9.
19. Ding X, Aoki V, Mascaro Jr JM, Lopez-Swiderski A, Diaz LA, Fairley JA. Mucosal and mucocutaneous (generalized) pemphigus vulgaris show distinct autoantibody profiles. J Invest Dermatol. 1997;109(4):592–6.
20. Beck Jr LH, Bonegio RG, Lambeau G, Beck DM, Powell DW, Cummins TD, et al. M-type phospholipase A2 receptor as target antigen in idiopathic membranous nephropathy. N Engl J Med. 2009;361(1):11–21.
21. Brouwer E, Tervaert JW, Horst G, Huitema MG, van der Giessen M, Limburg PC, et al. Predominance of IgG1 and IgG4 subclasses of anti-neutrophil cytoplasmic autoantibodies (ANCA) in patients with Wegener's granulomatosis and clinically related disorders. Clin Exp Immunol. 1991;83(3):379–86.
22. Gao Y, Ye H, Yu F, Guo XH, Zhao MH. Anti-myeloperoxidase IgG subclass distribution and avidity in sera from patients with propylthiouracil-induced antineutrophil cytoplasmic antibodies associated vasculitis. Clin Immunol. 2005;117(1):87–93.
23. Mellbye OJ, Mollnes TE, Steen LS. IgG subclass distribution and complement activation ability of autoantibodies to neutrophil cytoplasmic antigens (ANCA). Clin Immunol Immunopathol. 1994;70(1):32–9.
24. Liu LJ, Chen M, Yu F, Zhao MH, Wang HY. IgG subclass distribution, affinity of anti-myeloperoxidase antibodies in sera from patients with Wegener's granulomatosis and microscopic polyangiitis. Nephrology. 2008;13(7):629–35.
25. Engelmann R, Brandt J, Eggert M, Karberg K, Krause A, Neeck G, et al. IgG1 and IgG4 are the predominant subclasses among auto-antibodies against two citrullinated antigens in RA. Rheumatology (Oxford). 2008;47(10):1489–92.
26. Holland M, Hewins P, Goodall M, Adu D, Jefferis R, Savage CO. Anti-neutrophil cytoplasm antibody IgG subclasses in Wegener's granulomatosis: a possible pathogenic role for the IgG4 subclass. Clin Exp Immunol. 2004;138(1):183–92.
27. Hussain A, Pankhurst T, Goodall M, Colman R, Jefferis R, Savage CO, et al. Chimeric IgG4 PR3-ANCA induces selective inflammatory responses from neutrophils through engagement of Fcgamma receptors. Immunology. 2009;128(2):236–44.
28. Engelmann R, Eggert M, Neeck G, Mueller-Hilke B. The impact of HLA-DRB alleles on the subclass titres of antibodies against citrullinated peptides. Rheumatology (Oxford). 2010;49(10):1862–6.

29. van der Zee JS, van Swieten P, Aalberse RC. Inhibition of complement activation by IgG4 antibodies. Clin Exp Immunol. 1986;64(2):415–22.
30. Jefferis R, Reimer CB, Skvaril F, de Lange G, Ling NR, Lowe J, et al. Evaluation of monoclonal antibodies having specificity for human IgG sub-classes: results of an IUIS/WHO collaborative study. Immunol Lett. 1985;10(3–4):223–52.
31. van der Neut KM, Schuurman J, Losen M, Bleeker WK, Martinez-Martinez P, Vermeulen E, et al. Anti-inflammatory activity of human IgG4 antibodies by dynamic Fab arm exchange. Science. 2007;317(5844):1554–7.
32. Aalberse RC, Schuurman J. IgG4 breaking the rules. Immunology. 2002;105(1):9–19.
33. Hammarstrom L, Smith CI. IgG subclasses in bacterial infections. Monogr Allergy. 1986;19:122–33.
34. Escobar-Perez X, Dorta-Contreras AJ, Interian-Morales MT, Noris-Garcia E, Ferra-Valdes M. IgG2 immunodeficiency: association to pediatric patients with bacterial meningoencephalitis. Arq Neuropsiquiatr. 2000;58(1):141–5.

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ORIGINAL

Distribution of serum immunoglobulin G4 levels in Hashimoto's thyroiditis and clinical features of Hashimoto's thyroiditis with elevated serum immunoglobulin G4 levels

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Abstract. Immunoglobulin G4–related disease (IgG4-RD) is characterized by elevated serum IgG4 levels, IgG4-positive plasmacytes, and lymphocyte infiltration into multiple organs. IgG4 thyroiditis is a subset of patients with Hashimoto's thyroiditis (HT) who exhibited histopathological features of IgG4-RD; its source of serum IgG4 is suggested to be the thyroid gland. Although a relationship between IgG4-RD and IgG4 thyroiditis has been reported, the meaning of serum IgG4 in HT is uncertain. In this report, we prospectively evaluated serum IgG4 levels and clinical features of patients with HT. A total of 149 patients with HT were prospectively recruited into this study. According to the comprehensive diagnostic criteria of IgG4-RD, patients were divided into two groups: elevated IgG4 (>135 mg/dL) and non-elevated IgG4 (≤135 mg/dL). Median serum IgG4 levels of HT patients were 32.0 mg/dL (interquartile range, 20.0-65.0), with a unimodal non-normal distribution. Six patients (4.0%) had elevated serum IgG4 levels above 135 mg/dL. The elevated IgG4 group was older and exhibited enlarged hypoechoic areas in the thyroid gland, as revealed by ultrasonography, relative to the non-elevated IgG4 group. Levothyroxine (L-T4) replacement doses and titers of anti-thyroid antibodies did not differ significantly between the two groups. Two out of six HT patients with elevated serum IgG4 levels had extra-thyroid organ involvement as seen in IgG4-RD. In conclusion, HT patients with elevated serum IgG4 levels shared clinical features with both IgG4-RD and IgG4 thyroiditis. Longer follow-up periods and histopathological assessments are needed to further understand the meaning of elevated serum IgG4 levels in HT.

Key words: Immunoglobulin G4, IgG4 thyroiditis, Hashimoto's thyroiditis, Immunoglobulin G4-related disease, Prospective

IMMUNOGLOBULIN G4–RELATED DISEASE (IgG4-RD) is a recently proposed clinical entity, first reported in 2001 as a novel subtype of autoimmune pancreatitis [1]. The condition is characterized by elevated serum IgG4 levels, IgG4-positive plasmacytes, and lymphocyte infiltration into multiple organs, resulting in tissue fibrosis and organ dysfunction. In addition to the pancreas, the lacrimal gland, salivary gland, thyroid gland, biliary duct, and retroperitoneal tissue can also be involved in this disease [2].

The relationship between IgG4-RD and thyroid diseases has been previously investigated. About 19% of patients with IgG4-RD who also had hypothyroidism exhibited elevated thyroid volume and anti-thyroglobulin antibody (TgAb) and/or anti-thyroid peroxidase antibody (TPOAb) positivity. The thyroid function of these patients normalized after prednisolone treatment. The histology of their thyroid glands revealed IgG4-bearing plasma cells and loss of thyroid follicles; consequently, they were classified as having IgG4-related thyroiditis [3].

In cases of Riedel's thyroiditis, elevated serum IgG4 levels and/or an elevated number of IgG4-positive plasmacytes with dense fibrous tissue is observed in the thyroid gland, which responds to steroid therapy, reminiscent of the characteristics of IgG4-RD [4-6]. In addition, our group reported on the clinical implications of elevated serum IgG4 levels in Graves' disease (GD) [7].

Li and Kakudo *et al.* [8-10] reported IgG4 thyroid-

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itis in a subset of patients with Hashimoto's thyroiditis (HT) who exhibited histopathological features of IgG4-RD. In particular, they showed that IgG4 thyroiditis was associated with male gender, rapid progress, subclinical hypothyroidism, diffuse hypoechogenicity, and higher levels of circulating antibodies. They also demonstrated that the thyroid gland is the source of serum IgG4 in patients with IgG4 thyroiditis, based on the reduction in serum IgG4 levels after thyroidectomy.

Unfortunately, the meaning of serum IgG4 levels in HT is unclear because most previous reports were conducted retrospectively in a limited spectrum of HT. Therefore, in this study we prospectively evaluated the serum IgG4 levels and clinical features of 149 patients with HT. The purpose of our study was to clarify 1) the distribution of serum IgG4 in HT; 2) the association between serum IgG4 levels and clinical features in HT, compared with IgG4-related disease and IgG4 thyroiditis; and 3) the clinical features of HT patients with elevated serum IgG4.

Patients and Methods

Patients

A total of 149 patients with HT who had visited Wakayama Medical University from November 2011 to June 2014 were prospectively recruited to this study. Their clinical profiles, including family history of autoimmune thyroiditis (AITD), smoking, replacement doses of levothyroxine (L-T4), and laboratory data, were extracted from the electronic medical record. The diagnosis of HT was based on the guidelines for the diagnosis of chronic thyroiditis by Japan Thyroid Association: diffuse swelling of the thyroid gland without any other cause (such as Graves' disease) and with any one of the following laboratory findings [8]: 1) positive for anti-thyroid microsomal antibody or TPOAb, 2) positive for TgAb, and 3) lymphocytic infiltration in the thyroid gland confirmed with cytological examination. Patients who were pregnant or who had cancer, inflammatory disease, or thyroid nodules larger than 10 mm in diameter were excluded, because these factors could possibly affect serum IgG4 levels. None of the patients underwent surgery or radioiodine treatment. Patients were divided into two groups, those with elevated serum IgG4 levels (>135 mg/dL) and those with non-elevated serum IgG4 levels (≤135mg/dL), according to the currently established comprehensive diagnostic criteria for IgG4-RD [11]. Written informed consent was obtained from all patients, and the study protocol was approved by the Wakayama Medical University Hospital Ethics Committee (UMIN000016808).

Thyroid function tests and thyroid autoantibodies

Serum thyrotropin (TSH), free thyroxine (fT4), and free triiodothyronine (fT3) levels were measured by chemiluminescent immunoassay (Abbott Diagnostics, Tokyo, Japan). Reference ranges were defined as follows: TSH, 0.35–4.94 μIU/L; fT4, 0.70–1.48 ng/dL; and fT3, 1.71–3.71 pg/mL. Thyroid stimulating hormone receptor antibody (TRAb) was determined by enzyme-linked immunosorbent assay (Cosmic, Tokyo, Japan). TgAb and TPOAb were measured using an electrochemiluminescent immunoassay (SRL, Tokyo, Japan). Normal values were defined as follows: TRAb, < 1 IU/L; TgAb, < 28 IU/mL; and TPOAb, < 16 IU/mL. Thyroid stimulating antibody (TSAb) activities were determined using the TSAb bioassay kit (Yamasa, Choshi, Japan). Normal values for TSAb were defined as < 180%.

Serum IgG4 and IgG levels

Serum IgG4 and IgG levels were measured by a nephelometric immunoassay (BML, Osaka, Japan). Reference ranges for IgG4 and IgG were defined as 4–108 mg/dL and 870–1700 mg/dL, respectively. Because comprehensive diagnostic criteria for IgG4-RD include a serum IgG4 level > 135 mg/dL, we defined this as the cutoff value in this study [11].

Ultrasonographic evaluation

Ultrasonography was performed by conventional grayscale and color Doppler using a 10 MHz linear transducer (Toshiba Medical, Osaka, Japan). Hypoechogenicity in the thyroid gland was classified into four categories and scored as previously described [12]: Grade 0, diffuse high-amplitude echoes throughout the whole lobe of the thyroid; Grade 1, low-amplitude and non-uniform echoes throughout or in several regions of the thyroid; Grade 2, several sonolucent regions in the thyroid; and Grade 3, no apparent echoes or very low-amplitude echoes throughout the whole thyroid. Increase of color Doppler flow in the thyroid gland was determined as follows: 0, none; 1, mild; 2, moderate; and 3, severe. Thyroid size was measured as the sum of both lobes according to the following calculation: anteroposterior × transversal diameters (mm^2)

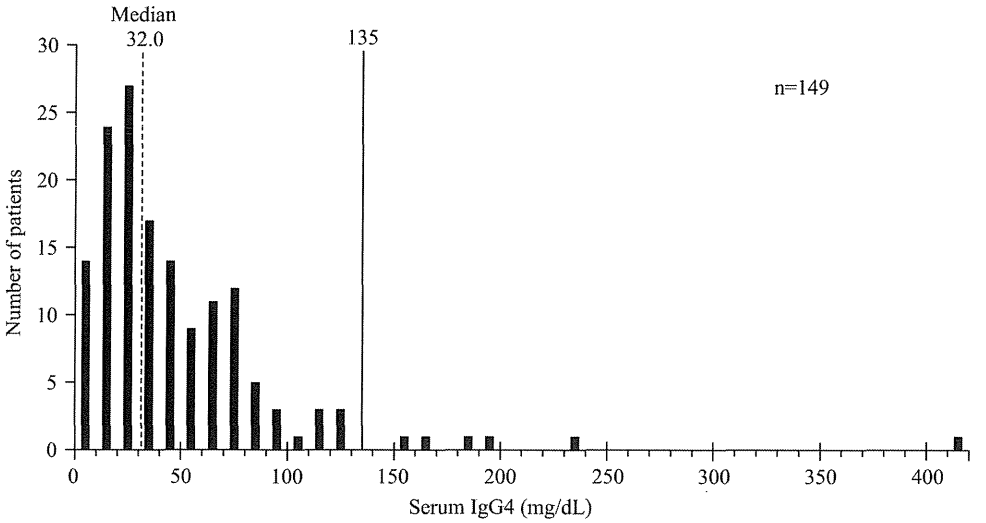

Fig. 1 Distribution of serum IgG4 levels in patients with HT
The dotted line indicates the median serum IgG4 level of all patients. The solid line indicates the cutoff value for serum IgG4 level according to the comprehensive diagnostic criteria for IgG4-RD.

at the maximum position [7, 13].

Statistical analysis

Sample size was calculated according to the previous report of IgG4 thyroiditis [10]. A total of 130 patients were required to provide at least 80% of power to detect the difference of clinical profiles such as age, anti-thyroid antibodies, and hypoechogenicity between IgG4 thyroiditis and non-IgG4 thyroiditis. Fisher's exact test was used to assess data in the two-dimensional contingency tables for comparison with sex, family history of AITD, and smoking. Mann–Whitney U-test was used for comparisons between two groups. Spearman's rank correlation coefficient (r_s) was determined to assess correlations between two variables. Data for TSH, TRAb, TgAb, and TPOAb were analyzed with log-transformed values. P-values < 0.05 were accepted as statistically significant (SPSS version 15, Chicago, IL). Data were presented as medians and interquartile ranges.

Results

The distribution of serum IgG4 levels in patients with HT

In 149 patients with HT, median serum IgG4 levels were 32.0 mg/dL (interquartile range, 20.0-65.0) with a unimodal non-normal distribution (Fig. 1). Six patients (4.0%) had elevated serum IgG4 levels above 135 mg/dL. Among those six, median serum IgG4 levels were 189.5 mg/dL (interquartile range, 172.8-222.0).

The association between serum IgG4 levels and clinical features, compared with IgG4 thyroiditis

A comparison of clinical features between the elevated and non-elevated IgG4 groups is shown in Table 1. The age of the elevated IgG4 group was significantly higher than that of the non-elevated IgG4 group. The elevated IgG4 group consisted of 3 males and 3 females, whereas the non-elevated IgG4 group consisted of 33 males and 110 females; however, the gender composition of the two groups did not differ significantly. In addition, there was no significant difference between the groups in the replacement doses of L-T4 or the titers of anti TgAb and TPOAb. Although ultrasonography revealed no significant difference in thyroid size between the groups, the elevated IgG4 group had larger hypoechoic areas in the thyroid gland than the non-elevated IgG4 group.

Clinical features of six patients with elevated serum IgG4 levels

The clinical features of six patients with elevated serum IgG4 levels are summarized in Table 2. Patients 1, 2, 3 and 6 did not have extra-thyroid organ involvement.

In accordance with the diagnostic criteria for IgG4-RD, patients 4 and 5 probably had extra-thyroid

Table 1 Clinical backgrounds in patients with Hashimoto's thyroiditis

	Non-elevated IgG4 (≤135mg/dL, n=143, 96%)		Elevated IgG4 (>135mg/dL, n=6, 4%)		
	Median (interquartile range)	n	Median (interquartile range)	n	*p*-value
Sex (male/female)	33/110		3/3		0.152[a]
Familial history of AITD [n (%)]	11 (7.7%)		2 (33.3%)		0.087[a]
Smoking history [n (%)]	20 (14.0%)		2 (33.3%)		0.265[a]
Age (years)	60.0 (42.0-71.0)	143	75.5 (71.0-77.8)	6	**0.009[b]**
IgG4 (mg/dL)	31.0 (19.0-62.0)	143	189.5 (172.8-222.0)	6	NA
IgG (mg/dL)	1339.0 (1149.0-1564.0)	143	1399.0 (1325.0-1584.0)	6	0.352[b]
IgG4/IgG (%)	2.5 (1.5-4.4)	143	12.0 (11.5-13.1)	6	**0.032[b]**
Thyroid size in ultrasound (mm^2)[c]	537.6 (389.8-798.1)	117	488.2 (304.4-905.3)	5	0.755[b]
Degree of hypoechogenicity[d]	1.0 (0-3.0)	116	2.0 (1.0-3.0)	5	**0.014[b]**
Increase of color Doppler flow	0 (0-1.0)	116	0 (0-0)	5	0.426[b]
TSH (μIU/mL)	2.5 (1.3-4.3)	141	2.3 (1.3-23.5)	6	0.829[b]
fT3 (pg/mL)	2.8 (2.5-3.0)	92	2.7 (2.1-3.1)	5	0.585[b]
fT4 (ng/dL)	1.1 (1-1.2)	141	1.1 (1.0-1.3)	6	0.537[b]
TRAb (IU/L)	1.0 (1.0-1.0)	102	1.0 (1.0-1.0)	6	0.478[b]
TgAb (IU/mL)	313.4 (83.0-531.8)	134	370.2 (181.0-842.3)	6	0.707[b]
TPOAb (IU/mL)	142.2 (16.9-390.5)	136	71.6 (20.7-126.9)	6	0.487[b]
L-T4 (μg/day)[e]	0 (0-50.0)	129	37.5 (0-93.8)	6	0.288[b]

P-values were obtained using [a]Fisher's exact test, or [b]Mann–Whitney U-test; *p*-values < 0.05 were accepted as significant and are indicated above in bold. Values of <0.003, <0.4, <1.0, <5, <10, >30.0, >600, and >4000 were used in calculations as 0.003, 0.4, 1.0, 5, 10, 30.0, 600, and 4000, respectively. [c]Thyroid size was measured as the sum of both lobes according to the following calculation: anteroposterior × transversal diameters (mm^2) at the maximum position. [d]Hypoechogenicity in the thyroid gland was classified into four categories, Grades 0–3. Higher score indicates a larger hypoechoic area. [e]L-T4 doses were chosen to maintain euthyroid status for 1 year. AITD, autoimmune thyroid disease; L-T4, levothyroxine; NA, not applicable.

Table 2 Clinical features in six patients with elevated IgG4 levels

Patients	1	2	3	4	5	6
Age (years) / Sex	61 / M	77 / M	70 / F	78 / F	74 / M	82 / F
TSH (μIU/L)[a]	96.4	30.5	2.4	2.7	1.1	1.9
fT3 (pg/mL)[a]	2.05	1.56	2.88	2.66	N.D.	3.06
fT4 (ng/dL)[a]	0.60	1.03	1.11	0.98	1.30	1.32
TRAb (IU/L)[a]	<1.0	<1.0	<1.0	<1.0	<1.0	<1.0
TSAb (%)[a]	N.D.	N.D.	123	118	N.D.	N.D.
TgAb (IU/mL)[a]	553	>4000	251	179	939	93
TPOAb (IU/mL)[a]	600.0	311.0	14.3	138.0	93.4	49.8
IgG4 (mg/dL)	153	232	192	416	168	187
IgG (mg/dL)	1312	4532	1434	1470	1364	1634
IgG4/IgG (%)	11.7	5.1	13.4	28.3	12.3	11.4
Thyroid size on US (mm^2)	1400	304	905	488	288	N.D.
Hypoechogenicity on US	3	2	1	1	3	N.D.
L-T4 (μg/day)	100	150	0	0	100	0
Follw-up (years)	2.5	3.1	2.2	1.9	1.8	1.0
Extra-thyroid organ involvement	-	-	-	Lacrimal glands	Pituitary	-
Follw-up IgG4 (mg/dL), periods after first admission	105, 2yr	N.D.	208, 8mo	N.D.	205, 1.5yr	N.D.

[a]Thyroid function was tested on their first visit to our hospital. M, male; F, female; N.D., not determined.

organ involvement. Patient 4 exhibited swelling of her bilateral eyelids and lacrimal glands, detected by CT and MRI. A complication of IgG4-related dacryoadenitis (Mikulicz disease) and HT was suspected, but histological confirmation was not yet obtained. Although patient 5 had the highest levels of serum IgG4, her titers of anti-thyroid antibodies were not highest in the group, and no replacement of L-T4 was needed. Patient 5 was hospitalized at our hospital because of anorexia and hyponatremia. On his first admission, he had hyponatremia (Na 116 mEq/L) with excess of urinary sodium excretion (U-Na 41 mEq/L), eosinophilia (WBC 5400/μL, Eosinophil 7.8%), and low cortisol level (ACTH 24.7 pg/mL, Cortisol 1.7 μg/dL), suspected of being adrenal insufficiency. Since his anterior pituitary hormone response to hormone provocative tests with CRH, TRH, and GnRH was low, he was diagnosed with hypopituitarism. His brain MRI exhibited swelling of the pituitary gland, probably due to pituitary adenoma or hypophysitis. Therefore, 15 mg of hydrocortisone was administered to treat his adrenal insufficiency, and to assess whether the swelling of the pituitary gland would shrink in response to hydrocortisone. Basal pituitary hormone levels and the size of the pituitary gland had not changed for about two years since his first visit.

Three patients out of six were followed their serum IgG4 levels within two years as shown in Table 2. The serum IgG4 level in patient 1 decreased to 105 mg/dL (≤135mg/dL) after treatment with L-T4 while maintaining a euthyroid state for two years. The serum IgG4 level in Patient 3 and 5 were slightly increasing during their clinical course. None of the patients experienced exacerbation of thyroid swelling or thyroid function during the follow-up period, and no patients needed thyroidectomy.

Discussion

Among the HT patients in our study, 4.0% had elevated serum IgG4 levels; this proportion was higher in a previous study conducted by Kawashima *et al.* (20.8%) [14]. This difference can be attributed in part to the method of screening patients: although Kawashima *et al.* excluded patients with normal serum IgG levels, we selected all patients with HT prospectively; consequently, we included patients with early-stage HT.

Li and Kakudo *et al.* [8-10] reported IgG4 thyroiditis in a subset of patients with HT who exhibited histopathological features of IgG4-RD. They showed that IgG4 thyroiditis was associated with younger age, male gender, subclinical hypothyroidism, higher levels of circulating antibodies, and diffuse hypoechogenicity. In their reports, the patients underwent total thyroidectomy due to marked swelling, tracheal stenosis, suspicion of malignancy, etc., and were diagnosed with IgG4 thyroiditis histopathologically. In our prospective study, most patients with HT had no airway symptoms and did not undergo thyroidectomy. The patients in the elevated IgG4 group were defined serologically with cutoff values of serum IgG4 levels above 135 mg/dL. Thus, patient background differed between the studies. An association between IgG4 thyroiditis and male predominance or diffuse hypoechogenicity has also been suggested in other reports [7, 14]. Consistent with those studies, ultrasonography revealed that hypoechoic areas were larger in the elevated IgG4 group than in the non-elevated IgG4 group in our prospective study. Because hypoechoic areas in ultrasonography have been suggested to be the infiltration of lymphocytes and fibrosis [15], we speculate that a higher grade of hypoechogenicity reflects greater infiltration of IgG4-positive plasma cells in the lesion. Male predominance was not confirmed statistically in this study.

In our prospective study, all patients in the elevated IgG4 group were above the age of 60, and the median age was higher in the elevated IgG4 group than in the non-elevated IgG4 group. This is consistent with observations made in GD and IgG4-RD [2, 7], but inconsistent with past reports of IgG4 thyroiditis [8-10]. Thus, this result implies that the elevated IgG4 group consists of patients with heterogeneous diseases, including IgG4-RD.

Replacement doses of L-T4 were not significantly higher in the elevated IgG4 group than in the non-elevated IgG4 group. This result was also inconsistent with characteristics of IgG4 thyroiditis in previous reports [8-10]; this discrepancy can be attributed to differences in the backgrounds of patients who had large goiters and needed thyroidectomy. Although some of the patients had received replacement doses of L-T4 during their first visit to our hospital, withdrawal of L-T4 was not tried to estimate thyroid function status.

Previous reports have discussed the association between serum IgG4 levels and anti-thyroid antibodies; in particular, these studies have shown that IgG4 is a predominant subclass of anti TgAb and TPOAb

in patients with HT [16-20]. In addition, the titers of serum anti-thyroid antibodies in patients with IgG4 thyroiditis are higher than in patients with non-IgG4 thyroiditis [8-10, 14]. On the other hand, one clinical study showed no significant difference in serum IgG levels between IgG4 thyroiditis and non-IgG4 thyroiditis [18]. Recently, Li *et al.* [16] demonstrated a negative correlation between serum IgG4 and titers of anti TgAb and TPOAb in patients with HT, despite the predominance of the IgG4 subclass in both antibodies. Therefore, it remains controversial whether serum IgG4 levels correspond with titers of anti-thyroid antibodies. In this study, titers of anti-TgAb and TPOAb did not differ significantly between the elevated IgG4 group and non-elevated IgG4 group, nor did they correlate with serum IgG4 levels. Further prospective studies will be needed in order to evaluate the association between serum IgG4 levels and titers of anti-thyroid antibodies.

It has been reported that some patients with IgG4 thyroiditis who had initially treated as GD and rapidly developed hypothyroidism after ATD treatment [14, 21]. In our report, no patients in the elevated IgG4 group had a medical history of GD, and their titers of TRAb and TSAb were negative as shown in Table 2.

In our study, two patients in the elevated IgG4 group exhibited involvement of extra-thyroid organ, as seen in IgG4-RD, implying that the extra-thyroid organ was the source of serum IgG4. However, previous reports suggested that the thyroid gland is the source of serum IgG4 in patients with IgG4 thyroiditis, based on the reduction in serum IgG4 levels after thyroidectomy [8-10]. In these previous reports, no extra-thyroid organ involvement associated with IgG4-RD was observed in IgG4 thyroiditis. Accordingly, we speculate that elevated IgG4 group in HT is a heterogeneous in its origin of serum IgG4, which include IgG4-RD, IgG4 thyroiditis and non-specific IgG4 elevation with HT. Generally, histopathological findings are necessary for accurate diagnosis of these diseases. However, we could not conduct histopathological analyses, because there were no patients who needed tissue sampling or thyroidectomy in our cohort.

Time course of serum IgG4 during treatment and clinical course is not fully provided in our study, which may be essential to elucidate pathophysiological relationships and therapeutic outcomes of this new entity.

In summary, we prospectively evaluated the serum IgG4 levels and clinical features of patients with HT. A minority (4.0%) of the patients had serum IgG4 levels above 135 mg/dL. HT patients with elevated serum IgG4 levels shared clinical features with both IgG4-RD and IgG4 thyroiditis. Longer follow-up periods and histopathological assessments are needed to further understand the meaning of elevated serum IgG4 levels in HT.

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Disclosure Statement

No competing financial interests exist.

References

1. Hamano H, Kawa S, Horiuchi A, Unno H, Furuya N, et al. (2001) High serum IgG4 concentrations in patients with sclerosing pancreatitis. *N Engl J Med* 344: 732–738.
2. Stone JH, Zen Y, Deshpande V (2012) IgG4-related disease. *N Engl J Med* 366: 539–551.
3. Watanabe T, Maruyama M, Ito T, Fujinaga Y, Ozaki Y, et al. (2013) Clinical features of a new disease concept, IgG4-related thyroiditis. *Scand J Rheumatol* 42: 325–330.
4. Dahlgren M, Khosroshahi A, Nielsen GP, Deshpande V, Stone JH (2010) Riedel's thyroiditis and multifocal fibrosclerosis are part of the IgG4-related systemic disease spectrum. *Arthritis Care Res (Hoboken)* 62: 1312-1318.
5. Hennessey JV (2011) Clinical review: Riedel's thyroiditis: a clinical review. *J Clin Endocrinol Metab* 96: 3031-3041.
6. Fatourechi MM, Hay ID, McIver B, Sebo TJ, Fatourechi V (2011) Invasive fibrous thyroiditis (Riedel thyroid-

itis): the Mayo Clinic experience, 1976-2008. *Thyroid* 21: 765-772.
7. Takeshima K, Inaba H, Furukawa Y, Nishi M, Yamaoka H, et al. (2014) Elevated serum immunoglobulin G4 levels in patients with Graves' disease and their clinical implications. *Thyroid* 24: 736-743.
8. Li Y, Nishihara E, Hirokawa M, Taniguchi E, Miyauchi A, et al. (2010) Distinct clinical, serological, and sonographic characteristics of Hashimoto's thyroiditis based with and without IgG4-positive plasma cells. *J Clin Endocrinol Metab* 95: 1309–1317.
9. Li Y, Bai Y, Liu Z, Ozaki T, Taniguchi E, et al. (2009) Immunohistochemistry of IgG4 can help subclassify Hashimoto's autoimmune thyroiditis. *Pathol Int* 59: 636-641.
10. Kakudo K, Li Y, Taniguchi E, Mori I, Ozaki T, et al. (2012) IgG4-related disease of the thyroid glands. *Endocr J* 59: 273-281.
11. Umehara H, Okazaki K, Masaki Y, Kawano M, Yamamoto M, et al. (2012) Comprehensive diagnostic criteria for IgG4-related disease (IgG4-RD), 2011. *Mod Rheumatol* 22: 21-30.
12. Yoshida A, Adachi T, Noguchi T, Urabe K, Onoyama S, et al. (1985) Echographic findings and histological feature of the thyroid: a reverse relationship between the level of echoamplitude and lymphocytic infiltration. *Endocrinol Jpn* 32: 681–690.
13. Kitajima K, Takahashi S, Maeda T, Yoshikawa T, Ohno Y (2012) Thyroid size change by CT monitoring after sorafenib or sunitinib treatment in patients with renal cell carcinoma: comparison with thyroid function. *Eur J Radiol* 81: 2060-2065.
14. Kawashima ST, Tagami T, Nakao K, Nanba K, Tamanaha T, et al. (2014) Serum levels of IgG and IgG4 in Hashimoto thyroiditis. *Endocrine* 45: 236–243.
15. Werner SC (1977) Modification of the classification of the eye changes of Graves' disease: recommendations of the Ad Hoc Committee of the American Thyroid Association. *J Clin Endocrinol Metab* 44: 203–204.
16. Li W, Fan G, Chen L, Zhang R, Zhang K, et al. (2014) A new type of natural bispecific antibody with potential protective effect in Hashimoto thyroiditis. *J Clin Endocrinol Metab* 99: E1602-1609.
17. Forouhi NG, McLachlan SM, Middleton SL, Atherton MC, Baylis P, et al. (1987) T cell regulation of thyroglobulin autoantibody IgG subclasses in Hashimoto's thyroiditis. *Clin Exp Immunol* 69: 314-322.
18. Zhang J, Zhao L, Gao Y, Liu M, Li T, et al. (2014) A classification of Hashimoto's thyroiditis based on immunohistochemistry for IgG4 and IgG. *Thyroid* 24: 364-370.
19. Kohno Y, Kijima M, Yamaguchi F, Saito K, Tsunoo H, et al. (1993) Comparison of the IgG subclass distribution of anti-thyroid peroxidase antibodies in healthy subjects with that in patients with chronic thyroiditis. *Endocr J* 40: 317-321.
20. Xie LD, Gao Y, Li MR, Lu GZ, Guo XH (2008) Distribution of immunoglobulin G subclasses of antithyroid peroxidase antibody in sera from patients with Hashimoto's thyroiditis with different thyroid functional status. *Clin Exp Immunol* 154: 172-176.
21. Nishihara E, Hirokawa M, Takamura Y, Ito M, Nakamura H, et al. (2013) IgG4 thyroiditis in a Graves' disease patient with large goiter developing hypothyroidism. *Thyroid* 23: 1496–1497.

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ORIGINAL

Clinicopathological features of Riedel's thyroiditis associated with IgG4-related disease in Japan

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Abstract. Riedel's thyroiditis (RT) is a rare chronic fibrosing disorder characterized by a hard, infiltrative lesion in the thyroid gland, which is often associated with multifocal fibrosclerosis. Immunoglobulin G4–related disease (IgG4-RD) is typified by infiltration of IgG4-positive plasma cells into multiple organs, resulting in tissue fibrosis and organ dysfunction. In order to evaluate the clinicopathological features of RT and its relationship with IgG4-RD, we performed a Japanese literature search using the keywords "Riedel" and "Riedel's thyroiditis." We used the electronic databases Medline and Igaku Chuo Zasshi, the latter of which is the largest medical literature database in Japan. The diagnosis of RT was based on the presence of a fibroinflammatory process with extension into surrounding tissues. Only 10 patients in Japan fulfilled RT diagnostic criteria during the 25-year period between 1988 and 2012. Two patients with confirmed IgG4/IgG immunohistochemical findings demonstrated 43 and 13 IgG4-positive plasma cells per high-power field, respectively, and the IgG4-positive/IgG-positive plasma cell ratios of 20% and less than 5%. Of the 10 patients with RT, two received glucocorticoids, one of whom experienced marked shrinkage of the thyroid lesion. One patient had extra-thyroid involvement in the form of retroperitoneal fibrosis. Although the clinicopathological features of RT suggest that IgG4-RD may be the underlying condition in some cases, further investigation is needed to clarify the etiology of RT in relation to IgG4-RD.

Keywords: Riedel's thyroiditis, Immunoglobulin G4, Immunoglobulin G4–related disease, IgG4 thyroiditis, Japan

RIEDEL'S THYROIDITIS (RT) was first recognized in 1896 by Riedel as a hard, infiltrative lesion in the thyroid gland [1]. In 1985 the estimated incidence was 1.06 cases per 100,000 persons and the condition was found in 37 of 56,700 patients undergoing thyroidectomy, however, the precise incidence is not clear because of the rarity of this condition [2]. Histologically, RT manifests as a fibroinflammatory process with extension into surrounding tissues, inflammatory cell infiltrates, destruction of the thyroid follicles, and obliterative phlebitis [3-6]. The symptoms of RT, such as dyspnea, hoarseness, and dysphagia, are often due to local pressure or infiltration of the fibrotic process [7]. Systemic organ involvement, including retroperitoneal fibrosis, autoimmune pancreatitis, and sclerosing cholangitis, has also been reported [8-10].

An association between thyroid diseases such as Graves' disease, Hashimoto's thyroiditis, and RT and IgG4-related disease (IgG4-RD) has recently been reported [11-15]. Patients with IgG4-RD exhibit elevated serum IgG4 levels, IgG4-positive plasma cells, and tissue fibrosis and organ dysfunction caused by lymphocyte infiltration into multiple organs [16, 17]. Although RT and IgG4-RD share some similar histopathological features and both are associated with multifocal fibrosclerosis, the etiology of both diseases remains unclear [7, 18].

Since RT is such a rare disease, there have been only a few case reports in Japan. In order to evaluate the clinicopathological features of RT and its relationship

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with IgG4-RD, we performed a literature review of RT in Japan for the first time. Furthermore, we conducted IgG4-related immunohistochemical analyses concerning two selected cases.

Patients and Methods

Using the keywords "Riedel" and "Riedel's thyroiditis," we performed a literature search of the electronic databases Medline and Igaku Chuo Zasshi, the latter of which is the largest medical literature database in Japan. We identified 29 articles from Japan that were published between 1988 and 2012; five of these were excluded due to overlap. The remaining 24 papers were included in this study.

The authors of 14 papers agreed to cooperate with our survey of RT. We asked these authors to provide us with detailed information on each patient's clinical course and laboratory data, as well as histological findings of each thyroid gland. The diagnosis of RT was based on the presence of a microscopically or macroscopically confirmed fibroinflammatory process with extension into surrounding tissues; histopathological findings consisting of inflammatory cell infiltrates, destruction of the thyroid follicles, and obliterative phlebitis were considered ancillary information [8]. The differential diagnosis of RT included the following: solitary fibrous tumor, paucicellular type undifferentiated carcinoma, fibrous variant of Hashimoto's thyroiditis, sarcoma, diffuse sclerosing variant of papillary carcinoma, large cell lymphoma with sclerosis, and Hodgkin disease, nodular sclerosis type [19]. Thyroid function tests and anti-thyroid antibodies titers were evaluated based on the reference ranges of each institution.

Tissue specimens were available for two patients; immunohistochemical analysis of these specimen was conducted using anti-IgG (Nichirei, Tokyo, Japan, A57H, 1:1 dilution) and anti-IgG4 (Nichirei, Tokyo, HP6025, 1:2 dilution) antibodies. The total number of IgG4-positive plasma cells per high-power field (HPF) was counted and the IgG4/IgG ratio was calculated; both were compared to the comprehensive diagnostic criteria for IgG4-RD [20], which specify more than 10 IgG4-positive plasma cells per HPF and an IgG4/IgG ratio greater than 40%.

Results

Histopathological features of RT

The 24 papers we evaluated identified 10 patients who were diagnosed with RT based on the above mentioned criteria [8]. The remaining 14 patients, one of whom had suspected RT and IgG4-RD, were excluded from our study due to insufficient information. The histopathological features of 10 patients with RT, such as inflammatory cell infiltrates, destruction of the thyroid follicles and obliterative phlebitis, are shown in Table 1.

Immunohistochemical results from two patients demonstrated confirmed IgG4/IgG immunohistochemical findings, as shown in Fig. 1. The total number of IgG4-positive plasma cells in Patients 1 and 2 were 43/HPF and 13/HPF, respectively. The IgG4/IgG ratios were 20% in Patient 1 and less than 5% in Patient 2.

Clinical features of RT

Of the 10 RT patients, seven were women (Table 2).

Table 1 Pathological features in 10 patients with Riedel's thyroiditis

Patient	Age	Gender	Inflammatory cell infiltrates	Destruction of the thyroid follicles	Obliterative phlebitis	IgG4 (/HPF)	IgG4/IgG ratio (%)
1	31	M	+	+	+	43	20
2	27	F	+	+	+	13	< 5
3	89	F	+	+	+	N.D.	N.D.
4	38	F	+	+	+	N.D.	N.D.
5	50	F	+	N.D.	N.D.	N.D.	N.D.
6	46	F	+	N.D.	N.D.	N.D.	N.D.
7	54	F	+	+	+	N.D.	N.D.
8	65	F	+	+	N.D.	N.D.	N.D.
9	66	M	+	+	N.D.	N.D.	N.D.
10	53	M	+	N.D.	N.D.	N.D.	N.D.

HPF, high power field; N.D., not determined

All 10 patients were diagnosed with Riedel's thyroiditis based on the presence of a fibroinflammatory process with extension into surrounding tissues that was confirmed microscopically or macroscopically.

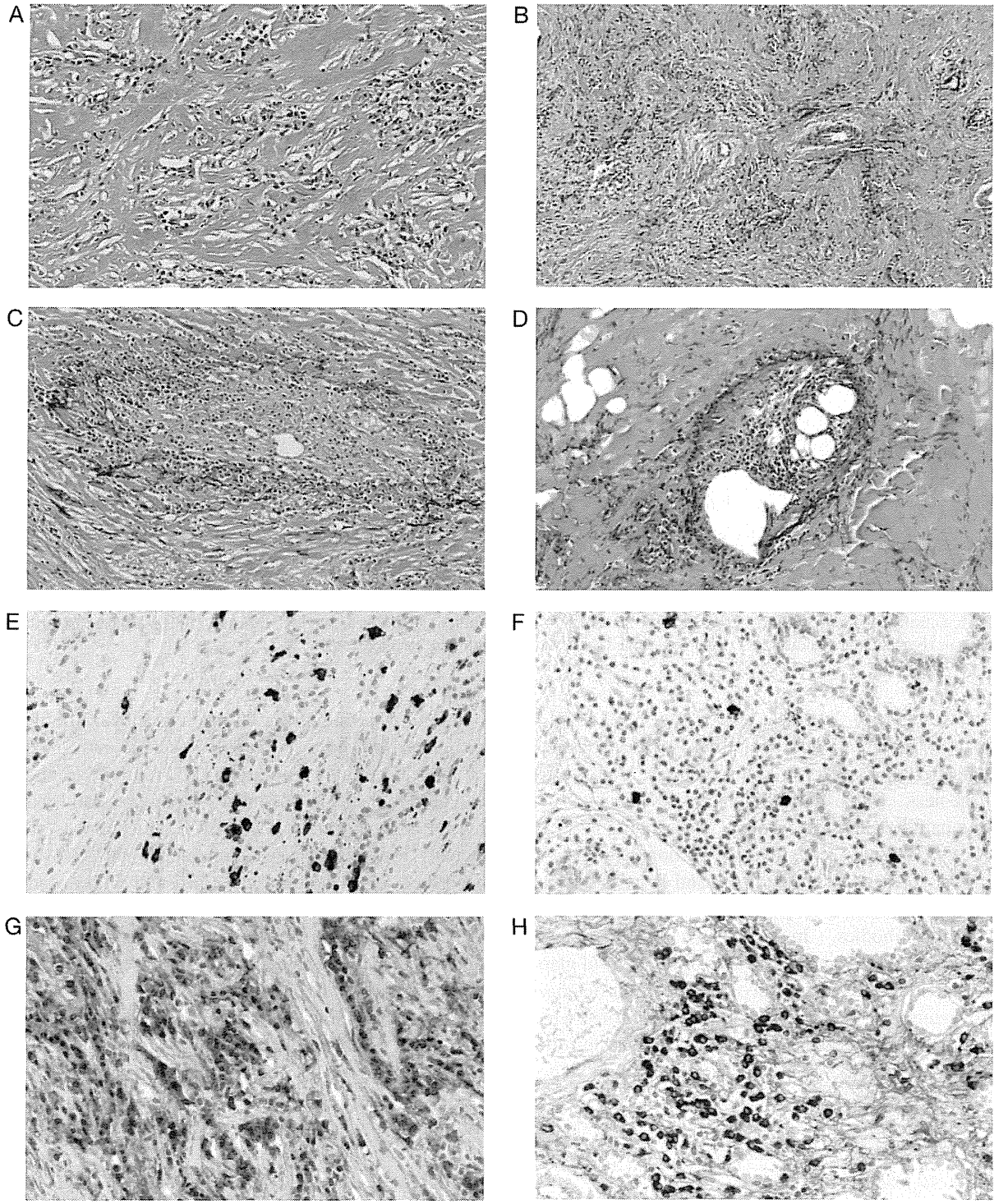

Fig. 1 Histopathology of Riedel's thyroiditis.
Histopathological images from Patient 1 (left column) and Patient 2 (right column) are shown.
Hematoxylin and eosin staining of the thyroid lesions revealed lymphoplasmacytic infiltration, severe fibrosis (A, B), and obliterative phlebitis (C, D). IgG4 immunostaining revealed the presence of IgG4-positive plasma cells (E, F). IgG immunostaining was also performed to calculate the ratio of IgG4-positive to IgG-positive plasma cells (G, H).

Table 2 Clinical features in 10 patients with Riedel's thyroiditis

Patient	Age	Gender	Symptoms	Thyroid function	Anti-thyroid antibodies (TgAb/ TPOAb)	Tg (ng/mL)	IgG4 (mg/dL)	IgG (mg/dL)	US	Treatment	Extrathyroid lesion
1	31	M	Neck swelling	Eu	- / -	62	N.D.	N.D.	Hypoechoic	Subtotal thyroidectomy	
2	27	F	Neck pain and neck swelling	Hyper	N.D. / -	36.9	N.D.	20.6	Hypoechoic	PSL 30 mg	
3	89	F	Dyspnea, hoarseness	Hypo	+ / N.D.	N.D.	N.D.	N.D.	Hypoechoic	PSL 30 mg	
4	38	F	Dysphagia, tenderness	Hyper	+ / +	Low	N.D.	N.D.	Heterogeneous	Isthmectomy	
5	50	F	Dysphagia, hoarseness	Hypo	- / -	N.D.	N.D.	N.D.	N.D.	Laser irradiation, stent placement	
6	46	F	Neck swelling	Eu	N.D. / -	130	N.D.	N.D.	Hypoechoic	Total thyroidectomy	
7	54	F	Neck swelling	Hypo	- / -	62.8	N.D.	N.D.	Hypoechoic	Subtotal thyroidectomy	
8	65	F	Neck swelling	Hyper	- / +	N.D.	N.D.	N.D.	Rough calcification	Lobectomy	
9	66	M	Neck mass	N.D.	N.D.	N.D.	N.D.	N.D.	Hypoechoic	Lobectomy	
10	53	M	Flank pain, neck mass	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	Lobectomy, steroid therapy	Retroperitoneal fibrosis

TgAb, anti-thyroglobulin antibody; TPOAb, anti-thyroid peroxidase antibody; Tg, thyroglobulin; Eu, euthyroidism; Hyper, hyperthyroidism; Hypo, hypothyroidism; N.D., not determined; US, ultrasonography; PSL, prednisolone.

The mean age at diagnosis was 51.9 yr (range, 27–89 yr). In most patients, symptoms such as dyspnea, hoarseness, and neck swelling were due to a mass effect in the neck. One patient presented to the hospital with flank pain due to retroperitoneal fibrosis with hydronephrosis. With respect to thyroid function, hypothyroidism was present in two patients and hyperthyroidism in four patients. Three patients were positive for anti-thyroid antibodies. In most cases, ultrasonography showed a severe hypoechoic area in the thyroid gland. Seven patients underwent thyroidectomy for diagnosis and treatment. Two patients received steroids, which resulted in marked shrinkage of the thyroid lesion in one patient. One patient had extra-thyroid involvement manifesting as retroperitoneal fibrosis.

The clinical course of the two patients with confirmed IgG4/IgG immunohistochemical findings are described below.

[Patient 1] A 31-year-old man presented with left neck swelling and aphagia. Palpation revealed a firm, immobile neck mass in his neck that was 9 cm in size. He was euthyroid (TSH, 1.52 μU/mL; free T4, 1.17 ng/dL). Anti-thyroid antibodies were negative, and thyroglobulin was 62 ng/dL. Ultrasonography of the thyroid gland showed a severely hypoechoic mass in the left lobe. Computed tomography (CT) showed tracheal deviation to the right, secondary to compression by the thyroid mass; tumor invasion of the trachea was suspected. Fine-needle aspiration biopsy (FNAB) was performed, and cytology was consistent with an adenomatous goiter. Although the cytology results were not malignant, the patient underwent subtotal thyroidectomy with neck dissection because the ultrasonography and CT findings were suspicious for malignancy. Intraoperatively, severe adhesions between the thyroid gland and surrounding tissues were found, leading to the excision of the thyroid tumor with the surrounding muscles and the trachea. The resected thyroid tumor was hard and yellowish-white in appearance. Microscopic evaluation revealed the presence of a fibroinflammatory process with extension into surrounding tissues, infiltrates of inflammatory cells, destruction of the thyroid follicles, and obliterative phlebitis was observed. The thyroid tumor was diagnosed as RT. Postoperatively, the patient did not experience recurrence of RT or the development of extra-

thyroid lesions.

[Patient 2] A 27-year-old woman with a known goiter presented with exacerbation of neck swelling and pain. Thyroid function testing revealed mild hyperthyroidism (TSH, 0.36 μU/mL; free T4, 1.11 ng/dL), but anti-TSH receptor antibodies were negative. Antithyroid antibodies were negative and thyroglobulin was 36.9 ng/dL. Ultrasonography of the thyroid gland showed a 2.5-cm hypoechoic mass in the left lobe. FNAB was performed twice, but cytology results of both procedures were inadequate for an accurate diagnosis. Since the patient's thyroid tumor was gradually growing, ^{99m}Tc/^{201}Tl scintigraphy was performed. The tumor was ^{99m}Tc negative and ^{201}Tl positive, which implied the possibility of malignancy. Thus, an open biopsy of the thyroid tumor was performed and the microscopic findings were identical to those in Patient 1. The thyroid tumor was diagnosed as RT. Consequently, the patient began a tapering course of prednisolone beginning at 30mg/day. One month after treatment, ultrasonography of her neck showed that the thyroid lesion had disappeared. Prednisolone was discontinued after seven months. Neither RT recurrence nor the development of extra-thyroid lesions was detected after steroid therapy.

Discussion

Based on the diagnostic criteria for RT mentioned above, only 10 patients fulfilled diagnostic criteria for RT in Japan during a 25-year period [3-6, 8]. Among the remaining 14 patients in the reports we evaluated, one had suspected RT and IgG4-RD, but we excluded this case because of the absence of extra-thyroid expansion [21].

An association between RT and IgG4-RD has been reported [7, 18]. IgG4-RD is characterized by elevated serum IgG4 levels, IgG4-positive plasma cells, and lymphocyte infiltration into multiple organs, resulting in tissue fibrosis and organ dysfunction [16, 17]. Both diseases exhibited similar histopathological features and are associated with multifocal fibrosclerosis [7].

In order to characterize the relationship between RT and IgG4-RD, we performed IgG4 staining of the thyroid lesions of two patients whose tissue specimens were available for IgG4. Although the presence of IgG4-positive plasma cells was detected in both patients, the comprehensive diagnostic criteria for IgG4-RD were only partially met [18]. In both patients, the total number of IgG4-positive plasma cells was more than 10/HPF, but the IgG4/IgG ratio was less than 40% in both patients.

Pusztaszeri *et al.* [22] reported a case of RT in which IgG4 staining revealed 70 IgG4-positive plasma cells/HPF within the thyroid lesion, and an IgG4/IgG ratio of 35% (<40%). In addition, Dahrgren *et al.* [18] reported three cases of RT. One patient's thyroid lesion had 53 IgG4-positive plasma cells/HPF (IgG4/IgG ratio, 80%) within the thyroid lesion, whereas the other two patients had 8/HPF (IgG4/IgG ratio, 50%) and 10/HPF (IgG4/IgG ratio, 20%), respectively. Fatourechi *et al.* [8] investigated 21 cases of RT and confirmed the presence of IgG4-positive plasma cells in two patients; there were a few such cells in one case and moderate numbers in the other. Thus, among the six previously reported cases and the two of our cases, only one patient met the comprehensive diagnostic criteria for IgG4-RD [20]. Severe fibrosis associated with RT may lead to less lymphoplasmacytic infiltration, which may result in these criteria not being met. On the other hand, diagnostic criteria for IgG4 thyroiditis used by Li *et al.* were IgG4-positive plasma cells/HPF >20 and IgG4/IgG ratio > 30% [11]. Thus, organ-specific cut-off values for the number of IgG4-positive plasma cells and the IgG4/IgG ratio may be needed for the thyroid gland, as discussed for other-specific lesions associated with IgG4-RD [23].

Most previous studies of RT have demonstrated serum IgG4 levels of less than 135 mg/dL, the cut-off value used as one of the diagnostic criteria for IgG4-RD [8, 18, 22]. In this retrospective study, serum IgG4 levels were not evaluated preoperatively in all of the patients.

While both RT and IgG4-RD have been reported to occur more frequently in patients with hypothyroidism and those who are highly positive for anti-thyroid antibodies, RT is more common in women between 30 and 50 years of age [8, 7, 24-26], and IgG4-RD has a higher incidence in men older than 50 years [17, 27]. Our 10 Japanese patients with RT were predominantly females (70%), aged 30 to 60 years, which was rather consistent with the clinical profile of RT. Only 38% of patients were positive for anti-thyroid antibodies, and both patients with IgG4-positive plasma cells in their thyroid glands were negative for anti-thyroid antibodies.

Of note, Patient 10 had retroperitoneal fibrosis, which is one of the various lesions seen in patients with IgG4-RD. It has been reported that approximately

30% of RT patients develop retroperitoneal or mediastinal fibrosis within 10 years, and therefore long-term follow-up of patients with RT is necessary to identify subsequent IgG4-related extra-thyroid lesions [2].

Steroid therapy has often been reported to be effective in RT [28, 29]. Patient 2 was treated with prednisolone, which lead to the disappearance of her thyroid lesion. Similarly, the retroperitoneal lesion of Patient 10 resolved following glucocorticoid therapy. Thus, extra-thyroid organ involvement and the presence of IgG4-positive plasma cells both predict a good response to steroid therapy in patients with RT. In patients refractory to the steroid therapy, tamoxifen and rituximab have been reported to be effective [7, 30, 31].

In patients with RT, lymphocytic infiltration including T cells, B cells and eosinophils were confirmed within the fibrotic areas of the thyroid [5]; eosinophils were suggested to play a central role in this context [32]. The cytokines from these lymphocytes, particularly transforming growth factor β (TGF-β), is a key factor in the pathogenesis of fibrosis [33]. Tamoxifen has been reported to be effective for the treatment of RT; one of the proposed mechanisms of the drug was a decline of TGF-β followed by the inhibition of fibroblast proliferation [34-36]. Also, in patients with IgG4-RD, cytokines released from type 2 helper T (Th2) and regulatory T (Treg) cells including TGF-β are overexpressed in the affected sites [17]. These cytokines contributes to eosinophilia, IgG4 class switch, and progression of fibrosis, which are thought to be possible mechanisms of association between IgG4-RD and RT.

Since RT is such a rare disease, immunohistochemical analyses were performed only in limited cases. In addition, long-term investigations are also needed.

For the first time we performed a literature review of cases of RT in Japan, and identified only 10 patients diagnosed pathologically during a 25-year period. In two patients, the infiltration of IgG4-positive plasma cells was confirmed, one of which exhibited good response to steroid therapy. Although these clinicopathological features suggest that IgG4-RD may be the underlying condition in some patients with RT, further investigation is required to understand the etiology of RT in relation to IgG4-RD.

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Conflict of Interest

None of the authors have any potential conflicts of interest associated with this research.

References

1. Riedel BM (1896) Die chronische, zur Bildung eisenharter Tumoren führende Entzündung der Schilddrüse. *Verh Dtsch Ges Chir* 25: 101–105 (In German).
2. Hay ID (1985) Thyroiditis: a clinical update. *Mayo Clin Proc* 60: 836-843.
3. Beahrs OH, Mcconahey WM, Woolner LB (1957) Invasive fibrous thyroiditis (Riedel's struma). *J Clin Endocrinol Metab* 17: 201-220.
4. Meijer S, Hausman R (1978) Occlusive phlebitis, a diagnostic feature in Riedel's thyroiditis. *Virchows Arch A Pathol Anat Histol* 377: 339-349.
5. Schwaegerle SM, Bauer TW, Esselstyn CB Jr (1988) Riedel's thyroiditis. *Am J Clin Pathol* 90: 715-722.
6. Harach HR, Williams ED (1983) Fibrous thyroiditis--an immunopathological study. *Histopathology* 7: 739-751.
7. Hennessey JV (2011) Riedel's thyroiditis: a clinical review. *J Clin Endocrinol Metab* 96: 3031-3041.
8. Fatourechi MM, Hay ID, McIver B, Sebo TJ, Fatourechi V (2011) Invasive fibrous thyroiditis (Riedel thyroiditis): the Mayo Clinic experience, 1976-2008. *Thyroid* 21: 765-772.
9. de Lange WE, Freling NJ, Molenaar WM, Doorenbos H (1989) Invasive fibrous thyroiditis (Riedel's struma): a manifestation of multifocal fibrosclerosis? A case report with review of the literature. *Q J Med* 72: 709-717.
10. Bartholomew LG, Cain JC, Woolner LB, Utz DC, Ferris DO (1963) Sclerosing cholangitis: its possible association with Riedel's struma and fibrous retroperitonitis. Report of two cases. *N Engl J Med* 269: 8-12.
11. Li Y, Nishihara E, Hirokawa M, Taniguchi E, Miyauchi A, et al. (2010) Distinct clinical, serological, and sonographic characteristics of Hashimoto's thyroiditis based

with and without IgG4-positive plasma cells. *J Clin Endocrinol Metab* 95: 1309–1317.
12. Li Y, Bai Y, Liu Z, Ozaki T, Taniguchi E, et al. (2009) Immunohistochemistry of IgG4 can help subclassify Hashimoto's autoimmune thyroiditis. *Pathol Int* 59: 636-641.
13. Kakudo K, Li Y, Taniguchi E, Mori I, Ozaki T, et al. (2012) IgG4-related disease of the thyroid glands. *Endocr J* 59: 273-281.
14. Takeshima K, Inaba H, Furukawa Y, Nishi M, Yamaoka H, et al. (2014) Elevated serum immunoglobulin G4 levels in patients with Graves' disease and their clinical implications. *Thyroid* 24: 736-743.
15. Kawashima ST, Tagami T, Nakao K, Nanba K, Tamanaha T, et al. (2014) Serum levels of IgG and IgG4 in Hashimoto thyroiditis. *Endocrine* 45:236-243.
16. Hamano H, Kawa S, Horiuchi A, Unno H, Furuya N, et al. (2001) High serum IgG4 concentrations in patients with sclerosing pancreatitis. *N Engl J Med* 344: 732-738.
17. Stone JH, Zen Y, Deshpande V (2012) IgG4-related disease. *N Engl J Med* 366: 539-551.
18. Dahlgren M, Khosroshahi A, Nielsen GP, Deshpande V, Stone JH (2010) Riedel's thyroiditis and multifocal fibrosclerosis are part of the IgG4-related systemic disease spectrum. *Arthritis Care Res (Hoboken)* 62: 1312-1318.
19. Papi G, LiVolsi VA (2004) Current concepts on Riedel thyroiditis. *Am J Clin Pathol* 121 Supple: S50-63.
20. Umehara H, Okazaki K, Masaki Y, Kawano M, Yamamoto M, et al. (2012) Comprehensive diagnostic criteria for IgG4-related disease (IgG4-RD), 2011. *Mod Rheumatol* 22: 21-30.
21. Nagashima T, Maruyama A, Takatori S, Saito M, Osuga J, et al. (2012) Subclinical Riedel's thyroiditis with hypothyroidism coexisting with Mikulicz's disease. *Rheumatol Int* 32:1851-1852.
22. Pusztaszeri M, Triponez F, Pache JC, Bongiovanni M (2012) Riedel's thyroiditis with increased IgG4 plasma cells: evidence for an underlying IgG4-related sclerosing disease? *Thyroid* 22: 964-968.
23. Deshpande V, Zen Y, Chan JK, Yi EE, Sato Y, et al. (2012) Consensus statement on the pathology of IgG4-related disease. *Mod Pathol* 25: 1181-1192.
24. Best TB, Munro RE, Burwell S, Volpé R (1991) Riedel's thyroiditis associated with Hashimoto's thyroiditis, hypoparathyroidism, and retroperitoneal fibrosis. *J Endocrinol Invest* 14: 767-772.
25. Julie C, Vieillefond A, Desligneres S, Schaison G, Grunfeld JP, et al. (1997) Hashimoto's thyroiditis associated with Riedel's thyroiditis and retroperitoneal fibrosis. *Pathol Res Pract* 193: 573-577.
26. Marín F, Araujo R, Páramo C, Lucas T, Salto L (1989) Riedel's thyroiditis associated with hypothyroidism and hypoparathyroidism. *Postgrad Med J* 65: 381-383.
27. Watanabe T, Maruyama M, Ito T, Fujinaga Y, Ozaki Y, et al. (2013) Clinical features of a new disease concept, IgG4-related thyroiditis. *Scand J Rheumatol* 42: 325–330.
28. Bagnasco M, Passalacqua G, Pronzato C, Albano M, Torre G, et al. (1995) Fibrous invasive (Riedel's) thyroiditis with critical response to steroid treatment. *J Endocrinol Invest* 18: 305-307.
29. Vaidya B, Harris PE, Barrett P, Kendall-Taylor P (1997) Corticosteroid therapy in Riedel's thyroiditis. *Postgrad Med J* 73: 817-819.
30. Few J, Thompson NW, Angelos P, Simeone D, Giordano T, et al. (1996) Riedel's thyroiditis: treatment with tamoxifen. *Surgery* 120:993-998.
31. Soh SB, Pham A, O'Hehir RE, Cherk M, Topliss DJ (2013) Novel use of rituximab in a case of Riedel's thyroiditis refractory to glucocorticoids and tamoxifen. *J Clin Endocrinol Metab* 98:3543-3549.
32. Heufelder AE, Goellner JR, Bahn RS, Gleich GJ, Hay ID (1996) Tissue eosinophilia and eosinophil degranulation in Riedel's invasive fibrous thyroiditis. *J Clin Endocrinol Metab* 81: 977-984.
33. Shock A, Rabe KF, Dent G, Chambers RC, Gray AJ, et al. (1991) Eosinophils adhere to and stimulate replication of lung fibroblasts 'in vitro'. *Clin Exp Immunol* 86: 185-190.
34. Clark CP, Vanderpool D, Preskitt JT (1991) The response of retroperitoneal fibrosis to tamoxifen. *Surgery* 109: 502-506.
35. Yasmeen T, Khan S, Patel SG, Reeves WA, Gonsch FA, et al. (2002) Clinical case seminar: Riedel's thyroiditis: report of a case complicated by spontaneous hypoparathyroidism, recurrent laryngeal nerve injury, and Horner's syndrome. *J Clin Endocrinol Metab* 87: 3543-3547.
36. Jung YJ, Schaub CR, Rhodes R, Rich FA, Muehlenbein SJ (2004) A case of Riedel's thyroiditis treated with tamoxifen: another successful outcome. *Endocr Pract* 10: 483-486.

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ORIGINAL ARTICLE

Recovery of renal function after glucocorticoid therapy for IgG4-related kidney disease with renal dysfunction

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Abstract
Background Although renal dysfunction in IgG4-related kidney disease (IgG4-RKD) shows rapid resolution with glucocorticoid therapy, little is known about the appropriate initial glucocorticoid dose for induction therapy or long-term renal outcome.
Methods We retrospectively examined the differences in recovery of renal function according to the dose of glucocorticoid used for induction therapy and the long-term renal outcome in 43 patients with definite IgG4-RKD (mostly IgG4-tubulointerstitial nephritis), in whom the estimated glomerular filtration rate (eGFR) before glucocorticoid therapy was <60 ml/min.
Results Most patients were treated with glucocorticoid alone and had been maintained on glucocorticoid. The initial dose of prednisolone employed was ≤0.6 mg/kg/day (mean 0.47) in 27 patients (group L), and >0.6 mg/kg/day (mean 0.81) in 16 patients (group H). In both groups, the pretreatment eGFR was significantly improved at 1 month after the start of glucocorticoid therapy and the degree of improvement showed no significant inter-group difference. Relapse of IgG4-RKD occurred in 16.7 % of the group L patients and 13.3 % of the group H patients ($p = 0.78$). Among 29 patients who were followed up for over 36 months (mean 74 months) and had been maintained on glucocorticoid, none showed progression to end-stage renal disease and there was no significant difference between eGFR at 1 month after treatment and eGFR at the last review.
Conclusion In glucocorticoid monotherapy for IgG4-RKD, a moderate dose is sufficient for induction, and recovery of renal function can be maintained for a long period on low-dose maintenance, although relapse can occur even in patients receiving maintenance therapy.

Keywords IgG4-related disease · Chronic kidney disease · Tubulointerstitial nephritis · Glucocorticoid · Follow-up

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Introduction

IgG4-related disease (IgG4-RD) is a recently recognized fibro-inflammatory condition that can affect multiple organs [1, 2]. It is characterized by fibrosis and a dense lymphoplasmacytic infiltrate including numerous IgG4-positive plasma cells, being usually manifested as tumefactive or hyperplastic lesions in the affected organs subjectively or by radiology. In IgG4-RD, a rapid response to glucocorticoid (GC) therapy is also reported to be characteristic, and