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 obliterator 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...
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 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, 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

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

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).
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, hyperthyroidism 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. Ultrasoundography 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 because the ultrasoundography 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 obliterator phlebitis was observed. The thyroid tumor was diagnosed as RT. Postoperatively, the patient did not experience recurrence of RT or the development of extra-

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

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.
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. Anti-thyroid 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 contribute 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.

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