Warthin-like papillary thyroid carcinoma with immunoglobulin G4-positive plasma cells possibly related to Hashimoto’s thyroiditis

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Abstract. Hashimoto’s thyroiditis with heavy lymphoplasmacytic infiltration is a common comorbidity of immunoglobulin G4 (IgG4)-related thyroiditis and Warthin-like papillary thyroid carcinoma (WL-PTC). We hypothesized that WL-PTC may have a strong association with IgG4-related thyroiditis. To validate this hypothesis, we clinically and immunohistochemically studied 17 WL-PTC cases. Fourteen patients (82.4%) had anti-thyroglobulin antibody and were confirmed to have Hashimoto’s thyroiditis through microscopic analysis. Among them, five (29.4%) had disease consistent with IgG4-related thyroiditis but did not exhibit a “storiform” pattern or obliterative phlebitis. IgG4-related diseases were not found in other organs. No cases with serum IgG4 level of >135 mg/dL were noted. A total of 94.1% of WL-PTC cases had IgG4-positive plasma cells (+PCs) in the stroma, and cases with rich IgG4+PCs were more frequently associated with Hashimoto’s thyroiditis than those with poor IgG4+PCs. In this study, all cases without Hashimoto’s thyroiditis had poor IgG4+PCs, and one of them did not exhibit IgG4+PCs in the stroma of WL-PTC. Nodal metastatic lesions were seen in eight cases, all of which were not WL-PTC. As such, we should consider that the Hashimoto’s disease with rich IgG4+PCs seen in our cases is representative of non-IgG4-related disease and not IgG4-related disease involving multiple organs. This study is the first to demonstrate the presence of IgG4+PCs in the stroma of WL-PTC. We concluded that the appearance of IgG4+PCs in the stroma of WL-PTC may be related to Hashimoto’s thyroiditis with rich IgG4+PC.

Key words: Thyroid, Immunoglobulin G4, Papillary carcinoma, Warthin-like variant
hypothesize that WL-PTC may have a strong correlation with IgG4-RT. To validate this hypothesis, we studied 17 WL-PTC cases clinically and immunohistochemically in this paper. This is the first report demonstrating the presence of IgG4+PCs in a stroma of WL-PTC.

**Materials and Methods**

The study protocol was reviewed and approved by the Institutional Review Board of Kuma Hospital (20170914-7). We reviewed 2,890 cases of resected and histologically diagnosed PTC at Kuma Hospital between January 2014 and December 2016. Among them, 17 cases (0.6%) were WL-PTC. The diagnostic criteria for WL-PTC were as follows: 1) overtly papillary growth pattern, 2) oncocytic cytoplasm, and 3) heavy lymphoplasmacytic infiltration (Fig. 1). Immunohistochemical staining of IgG (A57H; ready-to-use; Histofine, Tokyo, Japan) and IgG4 (HP6025; ready-to-use; Histofine, Tokyo, Japan) was performed using an automated Leica Bond-Max system and Bond Refine detection kit (Leica Microsystems, Wetzlar, Germany), respectively, according to the manufacturer’s recommendations. The number of IgG4+PCs and IgG-positive plasma cells (IgG+PCs) in the hot area of PTC was estimated, and the non-tumorous thyroid tissue was observed at 400× magnification [high-power field (HPF)]. The number of IgG4+PCs and IgG+PCs was calculated in the same fields. We defined cases with >100 IgG4+PCs per HPF and/or those with >40% IgG4+PC/IgG+PC ratio as rich IgG4+PC case. The remaining cases were defined as poor IgG4+PC case. The criteria for IgG4-RT proposed by Li et al. [9] were adopted: >20 IgG4+PCs per HPF and >30% IgG4+PC/IgG+PC ratio. Clinical data were obtained from medical records of Kuma Hospital. Statistical analysis was performed using Fisher’s exact test or student’s t-tests. Results with p values of less than 0.05 were considered statistically significant.

**Results**

Of the 2,890 cases reviewed, 17 patients, comprising 13 women and 4 men with a mean age of 52.2 years (range, 31–77 years), had WL-PTC. Serum thyroglobulin levels of these 17 patients ranged from 0.3 ng/mL to 469 ng/mL (mean: 44.5 ng/mL) and were slightly elevated in three patients. One case showed increased serum thyroid-stimulating hormone. No cases with serum IgG4 of >135 mg/dL were noted, and no significant decline in serum IgG4 was identified after WL-PTC resection. The clinical and pathological findings of the 17 patients with WL-PTC are shown in Table 1. Among the 17 patients, 14 (82.4%) were positive for anti-thyroglobulin antibody that were microscopically confirmed to be Hashimoto’s thyroiditis. Of these 14 patients with Hashimoto’s thyroiditis, five (29.4%) had disease consistent with IgG4-RT but did not exhibit a “storiform” pattern or obliterative phlebitis. IgG4-RD was not found in other organs. The sizes of the tumors were measured by ultrasound, and the largest dimension ranged from 6 mm to 32 mm (mean: 15.5 mm).

Microscopically, all 17 patients with WL-PTC had IgG+PCs in the stroma, with a mean of 247.5/HPF (range, 48–563/HPF) (Fig. 2A). Of them, 16 (94.1%) also had IgG4+PCs (Fig. 2B), which ranged from 4–225/HPF, except for one patient in which the stroma exhibited 146 IgG+PCs/HPF but not IgG4+PCs. Four and five patients exhibited >100 IgG4+PCs/HPF and >40.0% IgG4+PC/IgG+PC ratio, respectively. A total of 6 and 11 cases of rich and poor IgG4+PC were noted, respectively. No patients with stromal fibrosis such as desmoplastic change or “storiform” pattern were identified. Eight patients (47.1%) showed nodal metastasis, of which all lesions did not exhibit any appearance characteristic of WL-PTC. No patients with lymphatic invasion, vascular invasion, or distant metastasis at the time of the operation were identified.

The mean age of 59.2 years in rich IgG4+PC cases was slightly higher (48.5 years) than that in poor IgG4+PC cases.
cases. The percentage of men with rich and poor IgG4+PC was 50.0% and 9.0%, respectively, but no statistical significance was noted. Serum thyroglobulin (mean: 20.5 ng/mL) in rich IgG4+PC cases was significantly lower than that (mean: 57.5 ng/mL) in poor IgG4+PC cases (p < 0.01). All six WL-PTC cases with rich IgG4+PC were associated with Hashimoto’s thyroiditis, and four (66.7%) of them were IgG4-RT. Eight WL-PTC cases with poor IgG4+PC (72.7%) were associated with Hashimoto’s thyroiditis, and one (9.1%) of them was IgG4-RT. All three cases without Hashimoto’s thyroiditis were poor IgG4+PC cases, and one of them did not exhibit IgG4+PCs in the stroma of WL-PTC and Hashimoto’s thyroiditis. Tumor size in rich IgG4+PC cases tended to be slightly larger than that in poor IgG4+PC cases. No significant difference was noted in terms of the number of IgG+PCs between rich and poor IgG4+PC cases.

### Table 1  Clinical and pathological findings of the 17 patients with Warthin-like papillary thyroid carcinoma

<table>
<thead>
<tr>
<th></th>
<th>WL-PTC (n = 17)</th>
<th>Rich IgG4+PC cases (n = 6)</th>
<th>Poor IgG4+PC cases (n = 11)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean, years)</td>
<td>52.2 (31–77)</td>
<td>59.2 (31–77)</td>
<td>48.5 (31–65)</td>
</tr>
<tr>
<td>Female/male</td>
<td>13/4</td>
<td>3/3</td>
<td>10/1</td>
</tr>
<tr>
<td>Thyroglobulin (mean, ng/mL)</td>
<td>44.5 (0.3–469)</td>
<td>20.5 (0.3–72)</td>
<td>57.5 (0.6–469)</td>
</tr>
<tr>
<td>Increased serum TSH</td>
<td>1 (5.9%)</td>
<td>0 (0%)</td>
<td>1 (9.1%)</td>
</tr>
<tr>
<td>Serum IgG4 &gt;135 mg/dL</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Preoperative (mean, mg/dL)</td>
<td>29.7 (8.4–58.6)</td>
<td>38.3 (8.4–58.6)</td>
<td>26.5 (8.5–57.8)</td>
</tr>
<tr>
<td>Postoperative (mean, mg/dL)</td>
<td>27.7 (7.9–60.3)</td>
<td>37.5 (7.9–60.3)</td>
<td>24.0 (9.4–46.0)</td>
</tr>
<tr>
<td>Positive anti-thyroglobulin antibody</td>
<td>14 (82.4%)</td>
<td>6 (100%)</td>
<td>8 (72.7%)</td>
</tr>
<tr>
<td>IgG4-related thyroiditis</td>
<td>5 (29.4%)</td>
<td>4 (66.7%)</td>
<td>1 (9.1%)</td>
</tr>
<tr>
<td>IgG4-related disease in other organs</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Tumor size (mean, mm)</td>
<td>15.5 (6–32)</td>
<td>19.8 (10–32)</td>
<td>13.2 (6–30)</td>
</tr>
<tr>
<td>IgG4+ PC in WL-PTC (mean)</td>
<td>247.5 (48–563)</td>
<td>258.5 (48–514)</td>
<td>241.5 (48–563)</td>
</tr>
<tr>
<td>IgG4+ PC in WL-PTC (mean)</td>
<td>64.2 (0–225)</td>
<td>123.2 (32–225)</td>
<td>32.0 (0–59)</td>
</tr>
<tr>
<td>Lymphatic invasion</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Vascular invasion</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Nodal metastasis</td>
<td>8 (47.1%)</td>
<td>2 (33.3%)</td>
<td>6 (54.5%)</td>
</tr>
<tr>
<td>WL-PTC appearance</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
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<tr>
<td>Distant metastasis at operation</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
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</table>

IgG4, Immunoglobulin G4; WL-PTC, Warthin-like papillary thyroid carcinoma; PC, Plasma cells

Discussion

IgG4-RD is an immune-mediated condition comprised of a group of disorders that share particular pathologic, serologic, and clinical features [1, 2]. The three central pathologic features of IgG4-RD are a lymphoplasmacytic infiltrate rich in IgG4+PCs, a variable degree of fibrosis with a characteristic “storiform” pattern, and obliterator phlebitis. Most IgG4-RD shows an elevated serum IgG4 level (>135 mg/dL) and a good initial therapeutic response to glucocorticoids. This protean condition includes type 1 autoimmune pancreatitis, sclerosing cholangitis, Mikulicz disease, sclerosing sialadenitis, inflammatory orbital pseudotumor, retroperitoneal fibrosis, tubulointerstitial nephritis, and hypophysitis, among others.

In general, the pathological diagnosis of IgG4-RD requires an IgG4+PC/IgG+PC ratio of >40% as well as the three characteristic findings, namely, dense lympho-
plasmacytic infiltrate, fibrosis with storiform pattern, and obliterative phlebitis [1]. The number of required IgG4+ PCs per HPF depends on the organ and ranges from 10 IgG4+ PCs per HPF to 200 IgG4+ PCs per HPF [1]. IgG4-RT has been described as among the IgG4-RD in the thyroid [4-6, 8, 9]. However, the diagnostic criteria of IgG4-RT are yet to be defined. In this paper, we adopted the criteria proposed by Li et al. [8, 9] for IgG4-RT: IgG4+ PCs of >20 per HPF and an IgG4+ PC/IgG+ PC ratio of >30%. IgG4-RT was present in 29.4% of patients with WL-PTC. However, the lesions did not exhibit a “storiform” pattern, and obliterative phlebitis characteristic of IgG4-RD was also not observed. In addition, IgG4-RD was not found in other organs, and no patient had serum IgG4 level >135 mg/dL. A large number of conditions can be associated with increased numbers of IgG4+ PCs in tissue without the characteristic histopathological features of IgG4-RD (non-IgG4-RD), including oral inflammatory diseases, primary sclerosing cholangitis, anti-neutrophil cytoplasmic antibody-associated vasculitis, rheumatoid arthritis, inflammatory bowel disease, rhinosinusitis, Rosai-Dorfman disease, splenic sclerosing angiomatoid nodular transformation, cutaneous plasmacytosis, perforating collagenosis, and autoimmune atrophic gastritis [1]. We should consider that the Hashimoto’s disease with rich IgG4+ PCs seen in our cases are non-IgG4-RD and not IgG4-RD involving multiple organs.

Neoplastic conditions associated with IgG4+ PCs have been reported in sclerosing mucoepidermoid carcinoma of the salivary gland [14, 15], non-small-cell lung cancers [16], extrahepatic cholangiocarcinoma [17], gastric cancer [18] and Warthin tumor [19]. The exact prevalence and nature of this phenomenon are still uncertain. In 2011, Ito et al. reported a case of PTC associated with IgG4-related sialoadenitis [20]. In the case, tumor nests were surrounded by dense plasma cells with intermingling fibrosis and lymphoid follicles. Approximately 90% of plasma cells expressed IgG4. IgG4+ PCs were even observed in the stroma of the metastatic lesion in the lymph nodes. However, the case was not WL-PTC and not associated with Hashimoto’s thyroiditis. Tasli et al. examined 59 cases of Hashimoto’s thyroiditis, in which 30 were associated with PTC, and demonstrated that 36.8% of non-IgG4-RT cases and 76.1% of IgG4-RT cases were associated with PTC [21]. The association of IgG4-RT with PTC is statistically significant (p < 0.004). However, the conclusion seems to be due to sampling bias, because most patients with IgG4-RT without PTC were excluded as controls in the study. In addition, the histology results of PTCs they examined showed that the cancer was classic or follicular variant and did not include WL-PTC.

In this study, 94.1% of the included WL-PTC cases had IgG4+ PCs in the stroma, and rich IgG4+ PC cases were more frequently associated with Hashimoto’s thyroiditis than poor IgG4+ PC cases. All three cases without Hashimoto’s thyroiditis were poor IgG4+ PC cases, and one of them did not exhibit Hashimoto’s thyroiditis and IgG4+ PCs in the stroma of WL-PTC. WL-PTC is frequently associated with Hashimoto’s thyroiditis and histologically shares an oncocytic cytoplasm and heavy

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**Fig. 2** Immunostaining for IgG (A) and IgG4 (B). Most IgG-positive plasma cells are also positive for IgG4 (Immunostain, 200×; A: IgG; B: IgG4).
lymphoplasmacytic infiltration with germinal centers with such disease [22]. We consider that the appearance of IgG4+ PCs in the stroma of WL-PTC is related to Hashimoto’s thyroiditis with rich IgG4+PC. This hypothesis is supported by the fact that the nodal metastatic lesions were not WL-PTC.

In conclusion, this study is the first to demonstrate the presence of IgG4+ PCs in the stroma of WL-PTC, which may be related to Hashimoto’s thyroiditis with rich IgG4+PC. In addition, we should consider that the Hashimoto’s disease with rich IgG4+PCs seen in our cases are non-IgG4-RD and not IgG4-RD involving multiple organs.

Disclosure

The authors have no conflicts of interest to declare regarding grant support or financial relationships.

References
