Papillary thyroid carcinoma with desmoid-type fibromatosis: A clinical, pathological, and immunohistochemical study of 14 cases

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Abstract. Papillary thyroid carcinoma (PTC) with desmoid-type fibromatosis (DTF) is characterized by genetic alterations of the fibroblasts. However, PTC-DTF is extremely rare, and the reports on such cases have been sporadic. Immunohistochemical staining using the antibody for beta-catenin is useful in diagnosing the variant. This report aims to describe the clinical, pathological, and immunohistochemical findings in 14 cases of PTC-DTF and to clarify the diagnostic significance of the variant. The patients included 9 women and 5 men, with a mean age of 49.3 years. PTCs with focal DTF components and with extensive DTF components included 7 cases each. No significant differences were noted in terms of age, gender, and serum thyroglobulin levels between extensive and focal DTF cases. On aspiration cytology, 12 cases were reported as suspicious for malignancy or malignant, and schwannoma or fibroma was suggested in 1 case each. The DTF components were histologically classified into 4 types, namely, central (4 cases), peripheral (1 case), mixed (7 cases), and diffuse type (2 cases). The stromal components were consistent with those of DTF. Immunohistochemically, fibroblasts in the DTF components showed nuclear and cytoplasmic expression for beta-catenin in 12 cases. The features are observed even in cases in which stromal components focally exist. Neither carcinoma cells nor the fibroblasts with Ki-67 labeling index >5% were found in all cases. We agree that PTC with nodular fasciitis-like stroma should be renamed to PTC-DTF.

Key words: Thyroid, Papillary carcinoma, Desmoid-type fibromatosis, Beta-catenin, Nodular fasciitis
A diagnosis of PTC-DTF was made on the basis of the presence of extensive proliferation of fibroblasts and myofibroblasts in the stroma of PTC. PTC cases with desmoplastic changes such as granulation tissue-like stroma were excluded. The cases were divided into two groups, namely, with focal DTF components and extensive DTF components, which occupied less than 50% and more than 50% of the tumor, respectively.

Clinical data were obtained from patients’ medical records at Kuma Hospital and National Hospital Organization Nagasaki Medical Center. The ultrasound results were interpreted based on sonographic patterns proposed by the 2015 American Thyroid Association Management Guidelines [6]. Fine-needle aspiration cytology (FNAC) was performed by using a 22-gauge needle under ultrasound guidance. Cytological slides were prepared by expressing the aspirated materials from the needle onto slide glasses and compressing them with a second slide, and they were immediately fixed with Cytorop (Alfresa Pharma Co., Osaka, Japan), a cytochemical fixative. They were stained using the Papanicolaou method. FNAC reports were categorized into nondiagnostic or unsatisfactory (ND/UNS), benign, atypia of undetermined significance or follicular lesion of undetermined significance (AUS/FLUS), follicular neoplasm or suspicious for a follicular neoplasm (FN/SFN), suspicious for malignancy (SFM), and malignant based on the criteria of The Bethesda System for Reporting Thyroid Cytopathology [7]. Histopathological features were assessed using hematoxylin eosin-stained sections from formalin-fixed, paraffin-embedded tissue. Representative tissue blocks were selected for immunohistochemical analysis. Immunohistochemical staining was performed using the automated Leica Bond-Max system and Bond Refine detection kit (Leica Microsystems, Wetzlar, Germany) according to the manufacturer’s recommendations. Primary antibodies used for immunohistochemical staining included beta-catenin (14, 1:400 dilution, BD Transduction Laboratories), CD34 (NU-4A1, 1:3 dilution, Nichirei, Tokyo, Japan), ER (6F11, 1:50 dilution, Dako, Newcastle, UK), and Ki-67 (MIB-1, 1:200 dilution, Dako, Glostrup, Denmark). Ki-67 labeling index (LI) was estimated by counting at least 500 carcinoma cells. A case of PTC with desmoplastic changes was used as control. Statistical analysis was carried out with the $\chi^2$ or Student’s t test. $p$ values < 0.05 were considered statistically significant.

**Results**

Clinical findings of PTC-DTF are shown in Table 1. The patients included 9 women and 5 men, with a mean age of 49.3 years (range, 19–77 years). No cases with a history of ionizing radiation exposure or

| Table 1 Clinical findings of papillary thyroid carcinoma with desmoid-type fibromatosis |
|---------------------------------------------|-----------|-----------|-----------|
|                                       | Total (n = 14) | Extensive DTF (n = 7) | Focal DTF (n = 7) |
| Age in years (mean)                  | 19–77 (49.3) | 29–68 (49.2) | 19–77 (49.3) |
| Male/female                          | 5/9         | 3/4        | 2/5        |
| Serum thyroglobulin (ng/ml)(mean)    | 3.1–444.1(79.6) | 3.1–188.5 (65.8) | 17.7–444.1 (102.5) |
| Free thyroxine (ng/dl)(mean)         | 0.82–2.55 (1.14) | 0.89–1.41 (1.08) | 0.82–2.55 (1.20) |
| Tumor size (mm)(mean)                | 16–79 (36.4) | 16–79 (41.6) | 20–42 (31.3) |
| Ultrasound examination                |            |           |            |
| High suspicion                       | 11         | 5         | 6          |
| Intermediate suspicion               | 3          | 2         | 1          |
| Low and very low suspicion           | 0          | 0         | 0          |
| Benign                               | 0          | 0         | 0          |
| Suspicious of nodal metastasis       | 7/14 (50.0%) | 4/7 (57.1%) | 3/7 (42.9%) |
| Aspiration cytology                  | (13)       | (6)       | (7)        |
| ND/UNS                               | 0          | 0         | 0          |
| Benign                               | 1          | 1         | 0          |
| AUS/FLUS                             | 0          | 0         | 0          |
| FN/SFN                               | 0          | 0         | 0          |
| SFM and Malignant                    | 12         | 5         | 7          |

**DTF, Desmoid-type fibromatosis; ND/UNS, Nondiagnostic or unsatisfactory; AUS/FLUS, Atypia of undetermined significance or follicular lesion of undetermined significance; FN/SFN, Follicular neoplasm or suspicious for a follicular neoplasm; SFM, Suspicious for malignancy.**
familial polyposis were included. Serum thyroglobulin levels ranged from 3.1 ng/mL to 444.1 ng/mL (mean 79.6 ng/mL) and were within normal limits (<46.5 ng/ml) in 8 (57.1%) cases. PTCs with focal DTF components and extensive DTF components included 7 cases each. No significant differences were noted in terms of the age, gender, serum thyroglobulin levels, and free thyroxine levels between the extensive and focal DTF cases. Ultrasonographically, the widest dimension of the tumors ranged from 16 to 79 mm (mean, 36.4 mm), and the interpretations were classified as high suspicion (11 tumors) or intermediate suspicion (3 tumors). Nodal metastasis was suggested in 7 cases (50.0%). On FNAC, 12 cases (92.3%) were reported as SFM or malignant, and PTC was suspected. One case with extensive DTF was reported as benign, and schwannoma or fibroma was suggested.

Grossly, the tumors were well demarcated but not encapsulated. The area of DTF was translucent, rubbery elastic, and tan in color (Fig.1). The border between DTF and conventional PTC was undefined, and it was difficult precisely to identify the area of DTF components.

The pathological findings are shown in Table 2. The mean proportion of extensive and focal DTF in PTC was 81.4 % (range, 60 to 95%) and 40.0% (range, 20 to 50%), respectively. Distribution of the DTF components was classified into 4 types, namely, central (4 cases), peripheral (1 case), mixed (7 cases), and diffuse type (2 cases).

**Table 2** Pathological finding of papillary thyroid carcinoma with desmoid-type fibromatosis

<table>
<thead>
<tr>
<th></th>
<th>Extensive DTF</th>
<th>Focal DTF</th>
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</thead>
<tbody>
<tr>
<td>Proportion of fibromatosis (mean)</td>
<td>60-95% (81.4%)</td>
<td>20-50% (40.0%)</td>
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<tr>
<td>Distribution of fibromatosis</td>
<td></td>
<td></td>
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<tr>
<td>Central</td>
<td>1</td>
<td>3</td>
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<tr>
<td>Periphery</td>
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<td>Mixed</td>
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<td>Diffuse</td>
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<td>0</td>
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<td>Encapsulation</td>
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<tr>
<td>Psammoma bodies</td>
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<tr>
<td>Intratumoral</td>
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<tr>
<td>Extratumoral</td>
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<td>Small-sized vessels with thick wall</td>
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<td>6</td>
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<tr>
<td>Intrathyroidal metastasis</td>
<td>2</td>
<td>4</td>
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<tr>
<td>Extrathyroidal invasion</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>Association with chronic thyroiditis</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Nodal metastasis</td>
<td>6/6</td>
<td>6/7</td>
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<tr>
<td>Central</td>
<td>(6/6)</td>
<td>(6/7)</td>
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<tr>
<td>Lateral</td>
<td>(4/4)</td>
<td>(3/5)</td>
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<tr>
<td>Presence of extranodal invasion</td>
<td>3/6</td>
<td>2/6</td>
</tr>
<tr>
<td>Presence of DTF</td>
<td>2/6</td>
<td>2/6</td>
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<tr>
<td>Distant metastasis</td>
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<tr>
<td>At operation</td>
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<td>0</td>
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<td>During follow-up</td>
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<td>Immunohistochemistry</td>
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<tr>
<td>PTCC</td>
<td>SC</td>
<td>PTCC</td>
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<tr>
<td>Beta-catenin$^a$</td>
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<td>7</td>
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<tr>
<td>ER</td>
<td>0</td>
<td>0</td>
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<tr>
<td>CD-34</td>
<td>0</td>
<td>0</td>
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<tr>
<td>Ki-67 labeling index (&gt;5%)</td>
<td>0</td>
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DTF, desmoid-type fibromatosis; $^a$, Nuclear and cytoplasmic staining; PTC, Papillary thyroid carcinoma; PTCC, Papillary thyroid carcinoma cells; SC, Stromal cells.
and mitotic Figures were not observed. The carcinoma cells were paucicellular in DTF areas and showed microfollicular pattern and/or small nest (Fig.3). The cytoplasm was moderately eosinophilic. The nuclei showed typical characteristics of PTC, except for ground-glass appearance. In non-DTF areas, the PTC histology was conventional type. Intratumoral and extratumoral psammoma bodies were present in 3 and 2 cases of PTC with focal DTF. Intrathyroidal metastasis and extrathyroidal invasion was commonly observed in PTC with focal DTF. Recurrent nerve invasion was noted in only 1 PTC with focal DTF case. Two cases had coincidentally separate conventional PTC. Five cases were associated with chronic thyroiditis. Nodal metastasis was demonstrated in 12 (92.3%) of 13 cases with lymph node resection. In 7 cases, the metastasis was present in both the central and lateral lymph nodes. The remaining 5 cases showed metastasis in only the central lymph nodes. Among them, pathological findings showed that 5 cases (3 PTC cases with extensive DTF and 2 PTC cases with focal DTF) showed extranodal invasion. In 4 cases (2 PTC cases with extensive DTF and 2 PTC cases with focal DTF), DTF components were observed in some of metastatic lesions in the lymph nodes (Fig.4); in these 4 cases, the numbers of lymph nodes with DTF components per the numbers of metastatic lymph nodes were 1/3, 3/21, 1/7, and 8/18, respectively. Distant metastasis was not detected at operation and during follow up in all cases.

Immunohistochemically, in 12 cases, nuclear and cytoplasmic staining of fibroblasts distributed in DTF components were positive for beta-catenin (Fig.5). In the remaining 2 PTC with focal DTF cases, fibroblasts showed cell membranous immunopositivity for the antibody. The fibroblasts seen in desmoplastic changes showed cell membranous immunopositivity for the antibody. The fibroblasts were negative for estrogen receptor or CD34. The carcinoma cells showed cell membranous immunopositivity...
PTC with desmoid-type fibromatosis

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The term DTF, rather than nodular fasciitis, is also preferred in immunohistochemical findings. A total of 80% of DTF show nuclear and cytoplasmic expression for beta-catenin, but such findings are not observed in nodular fasciitis [10]. We demonstrated that 12 (85.7%) of 14 PTC-DTF cases revealed nuclear and cytoplasmic expression for beta-catenin. Fibroblasts in desmoplastic changes showed cell membranous immunopositivity for the antibody. The findings may be useful in distinguishing between DTF components and desmoplastic changes. Lin et al. reported that the mean Ki-67 LI of nodular fasciitis and DTF were 23.71±15.01% and 3.20±1.26%, respectively [11]. In our study, stroma revealing >5% Ki-67 LI was not found. The findings also indicate DTF rather than nodular fasciitis.

The proportion of DTF in PTC is not defined. The stromal components usually accounted for more than 60% of the tumor mass [2, 12-14]. In our study, cases in which DTF components occupied less than 50% of the tumor mass were included. Even in such cases, the stromal components revealed nuclear and cytoplasmic immunoreactivity for beta-catenin and harbored a heterozygous somatic activating mutation in the corresponding CTNNB1 gene [5].

We agree with the proposal by Rebecchini et al. [5]. Microscopically, the stromal component is consistent with DTF and not with nodular fasciitis. Nodular fasciitis is composed of plump, immature, spindled to stellate fibroblasts or myofibroblasts in a myxoid stroma with granulation tissue-like vascular proliferation lymphocytes and extravasated red blood cells, and clinically reveals rapid growth but is reactive [8]. The findings are similar to desmoplastic changes seen in PTC used as control case in our study. Meanwhile, DTF has clonal fibroblastic proliferation and is composed of elongated, slender, and spindle-shaped cells of uniform appearance in a collagenous stroma [9]. DTF is usually more collagenous and less cellular than nodular fasciitis [9]. Thick-walled blood vessels sharply outlined from the surrounding tissue are also characteristic of DTF [9]. The stromal components seen in PTC we examined in this study were completely consistent with those of DTF.

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Discussion

In 1991, Chan et al. [1] first described 3 cases of PTC with exuberant nodular fasciitis-like stroma. Subsequently, PTC cases with similar stromal findings have been sporadically reported, and most of them were termed as PTC with nodular fasciitis-like stroma [3]. Recently, Rebecchini et al. reported 2 cases of PTC with nodular fasciitis-like stroma [5]. In the report, they proposed that the variant should be renamed PTC-DTF because the mesenchymal component showed aberrant nuclear and cytoplasmic immunoreactivity for beta-catenin and harbored a heterozygous somatic activating mutation in the corresponding CTNNB1 gene [5].

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be determined. In this study, the DTF components were present within nodal metastatic lesions in 4 of 12 cases. Toti et al. have reported similar findings [15]. The DTF components may possess metastatic capability or be induced by metastatic PTC in the lymph node.

Clinical features of PTC-DTF are not well documented. In our report, 5 (35.7%) of 14 patients were men. Comparing with conventional PTC, PTC-DTF tends to be prevalent in men. On ultrasound examination, the variant has been occasionally interpreted as intermediate suspicion [15, 18, 19]. Yang et al. reported a case of PTC-DTF with cytological interpretation of a malignant neoplasm most consistent with myxoid sarcoma, and they discussed the potential pitfalls in FNAC [2]. In 1 of our cases, schwannoma or fibroma was suggested. Desmoid tumors have been frequently confused with such mesenchymal tumors [20]. PTC-DTF should be considered as the differential diagnoses of sarcoma, fibroma, or schwannoma on thyroid FNAC. In our study, this variant frequently revealed nodal metastasis, but appears unaggressive because of the absence of distant metastasis and low Ki-67 LI.

In conclusion, we agree that PTC with nodular fasciitis-like stroma should be renamed PTC-DTF. PTC-DTF is a rare variant of PTC characterized by the genetic alteration of fibroblasts and is clinically not aggressive. Its features are observed even in cases in which the stromal components focally exist. On FNAC, the variant may be confused with mesenchymal tumors. Immunohistochemical staining using the antibody for beta-catenin is useful in diagnosis.

Disclosure

The authors declare no conflicts of interest.

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