Clinicopathologic Significance of Intrathyroidal Epithelial Thymoma/Carcinoma Showing Thymus-like Differentiation

A Collaborative Study With Member Institutes of the Japanese Society of Thyroid Surgery

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Abstract

Intrathyroidal epithelial thymoma (ITET)/carcinoma showing thymus-like differentiation (CASTLE) is a rare malignant neoplasm of the thyroid resembling lymphoepithelioma-like and squamous cell carcinoma (SCC) of the thymus. This disease was initially proposed by Miyauchi et al1 in 1985 as ITET, which should be differentiated from SCC of the thyroid. Rosai2 accepted it as a novel neoplastic entity of the lower neck, and Chan and Rosai3 denominated it as carcinoma showing thymus-like differentiation. Recently, this disease has been designated as an independent clinicopathologic entity of thyroid tumors in the newest edition of the World Health Organization classification of tumors of endocrine organs.4

This disease is thought to originate from ectopic thymic tissue or remnants related to thymic development in or adjacent to the thyroid because the tumor usually occurs in the lower part, especially the lower pole, of the thyroid and shows several features of thymic differentiation, such as the following: (1) lobulation on cut surfaces; (2) an expansive growth pattern; (3) thick, fibrous bands dividing the tumor cell nests; (4) the presence of many lymphocytes; (5) perivascular spaces with lymphocytes; (6) rare or infrequent mitoses; and (7) oval, vesicular nuclei, sharply defined nucleoli, and pale cytoplasm. Furthermore, lack of foci of papillary, follicular, medullary, or anaplastic carcinoma is also an important characteristic.1,2,5,6

The most important differential diagnoses include primary SCC of the thyroid, undifferentiated carcinoma with squamoid features, and metastatic SCC from other organs because ITET/CASTLE may histologically resemble these diseases and may even include foci of squamous differentiation.3,7 This distinction is important because ITET/CASTLE has different biologic behavior and a more favorable prognosis than these carcinomas.3,7,8

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To date, clinicopathologic features of ITET/CASTLE have not been studied in depth, and the survival curve for patients has not been reported because of its rarity and difficulty in diagnosis. In the present study, therefore, we obtained 25 cases of ITET/CASTLE in cooperation with the member institutes of the Japanese Society of Thyroid Surgery (JSTS) and studied their clinicopathologic features.

Materials and Methods

Cases and Tissue Specimens

To study the pathologic features and clinical behavior of ITET/CASTLE, a questionnaire survey was conducted among member institutes of JSTS before the 38th annual meeting of JSTS. We asked the participants to submit cases diagnosed by the pathologists at their institutes as ITET/CASTLE and those as carcinoma showing squamoid differentiation with or without an undifferentiated carcinoma component because we thought that some ITET/CASTLE cases might be included in the latter series. Cases extended or metastasized from other organs or papillary carcinomas with squamous metaplasia were excluded. In total, 96 cases were submitted. We collected clinical data, H&E-stained sections, and, if available, 10 slides of unstained sections from representative formalin-fixed, paraffin-embedded blocks for immunohistochemical staining for each case.

The study was approved by the ethical committee of each hospital, and informed consent was obtained from the participating patients by a written acceptance form. The H&E-stained sections were reviewed by 2 pathologists (Y.N. and K. Kakudo) and the author who originally identified this entity (A.M.) without knowledge of clinical data including patient prognoses and classified these lesions into the following categories: ITET/CASTLE, 25 cases; carcinoma showing squamoid differentiation with and without undifferentiated carcinoma component, 19 and 26 cases, respectively; and “others,” 26 cases, most of which were diagnosed as undifferentiated carcinoma without squamoid differentiation or neoplasms of stromal origin.

For the 25 cases of ITET/CASTLE, clinicopathologic data, therapeutic procedures performed, and clinical outcomes of patients were analyzed. Immunohistochemical studies were also performed for 23 cases of ITET/CASTLE from which unstained sections were available. Immunohistochemical staining for CD5 was also performed on 38 cases of other carcinoma showing squamoid features.

Immunohistochemical Staining

After establishing the diagnosis based on H&E-stained sections, immunohistochemical staining was performed for the following: CD5 as a marker for carcinoma of thymic origin and thyroglobulin and thyroid transcription factor-1 (TTF-1) as markers of follicular epithelium. A monoclonal antibody against CD5 (clone NCL-CD5-4C7, Novocastra, Newcastle upon Tyne, England) was applied at a dilution of 1:50. Monoclonal antibodies against thyroglobulin (clone Dak-Tg6, DAKO A/S, Glostrup, Denmark) and TTF-1 (clone 8G7G3/1, DAKO A/S) were diluted for use as primary antibodies at 1:200. Heat treatment at 121°C for 20 minutes in a pressure cooker was performed for immunohistochemical studies of CD5 and TTF-1. Immunohistochemical studies were performed with the EnVision polymer technique (DAKO A/S).

Immunohistochemical Evaluation

Immunohistochemical deposits for CD5 were observed predominantly in the cellular membranes, those for thyroglobulin were in the cytoplasm, and those for TTF-1 were in the nuclei. Cases were classified as positive when the lesions included any neoplastic cells clearly expressing these markers.

Postoperative Follow-up

Patients were followed up postoperatively for periods from 4 to 306 months (mean ± SD, 96.0 ± 70.5 months). The Kaplan-Meier method was used to calculate the overall survival rate.

Statistical Analyses

The Fisher exact probability test, χ² test, and log-rank test were used to examine the relationships between variables and to evaluate the clinical outcome of patients. A P value less than .05 was considered significant.

Results

Pathologic Findings and Immunohistochemical Results

Macroscopically, ITET/CASTLE tumors were well-defined, lobulated, and pinkish gray, and usually located in the lower part of the thyroid. Of the 96 cases, 25 were diagnosed as ITET/CASTLE based on the findings of H&E-stained sections. The typical histologic characteristics of ITET/CASTLE in our series were as follows: (1) lobular architecture with fibrous bands separating solid islands of epithelial cells, with well-bordered sheet or solid nest appearances; (2) peritumoral and intratumoral infiltration of many lymphocytes and plasma cells; and (3) tumor cells that were spindle, squamoid, or polygonal, with pale cytoplasm and oval, vesicular nuclei having well-defined nucleoli. Occasionally, squamoid or spindle-shaped epithelial cells with whorls resembling Hassall corpuscles were observed. These features resembled thymoma, especially of cortical origin (World Health Organization classification type B2). The
degree of squamous differentiation varied among the cases. Image 1B, Image 1C, and Image 1D show the typical H&E staining profiles of ITET/CASTLE.

The expression of markers useful for diagnosing ITET/CASTLE was analyzed immunohistochemically in 23 cases for which unstained tissue sections were available. For CD5 immunostaining, we excluded 6 cases from analysis because of a lack of CD5 immunoreactivity in intrinsic leukocytes that served as an internal control. We analyzed CD5 immunoreactivity in the remaining 17 cases and found 14 positive cases (82%) Image 1E and Image 1F. However, none of the 38 cases of carcinoma showing squamoid differentiation with or without an undifferentiated carcinoma component expressed CD5. Thus, the sensitivity and specificity of CD5 immunostaining for the diagnosis of ITET/CASTLE in the present series were 82% and 100%, respectively. Thyroglobulin and TTF-1 were negative in all cases of ITET/CASTLE as was carcinoma showing squamoid differentiation.

Patient Backgrounds and Preoperative Evaluations

The 25 patients with ITET/CASTLE in the present series were 11 men and 14 women (mean ± SD age, 52.4 ± 18.6
The subjective symptoms were neck tumor in 22 patients (88%) and hoarseness due to recurrent laryngeal nerve paralysis in 6 patients (24%). None of the patients complained of dyspnea. Tumors in 22 cases (92%) showed a hard consistency, and tumor mobility was poor in 16 cases (68%). However, none of the patients complained of rapid tumor enlargement. Calcification in the tumor lesion and leukocytosis, which are important features of SCC and anaplastic carcinoma, were lacking in all ITET/CASTLE cases. Fine-needle aspiration biopsy (FNAB) was performed in 20 cases. Only 1 patient was given a preoperative diagnosis of ITET/CASTLE. The remaining 19 were given a diagnosis of “suspicious” of thyroid carcinoma of an unusual type because their specimens showed unusual cytologic features different from those of papillary, follicular, medullary, and anaplastic carcinoma.

Intraoperative and Postoperative Findings for Patients With ITET/CASTLE

Of 25 ITET/CASTLE tumors, 23 (92%) were located in the lower part of the thyroid, and the location of 1 (4%) was unknown; 21 (84%) of 25 tumors did not coexist with thyroid nodules. Of the remaining 4 tumors, 2 (8%) were associated with benign thyroid nodule and 2 (8%) with papillary or follicular carcinoma, considered an incidental association. Surgical procedures for the 25 patients are summarized in Table 1. Of 23 patients, 22 (96%) underwent curative surgery, and 1 (4%) underwent palliative surgery only. Whether the surgery was curative was not stated in the questionnaires for the remaining 2 patients.

Lymph node metastasis was found in 9 (50%) of 18 patients who underwent lymph node dissection. The presence of metastasis was not indicated in the questionnaire for 1 patient, and metastases in the central and lateral compartments were observed in 7 and 5 patients, respectively. However, there were few metastatic nodes, and only 2 (11%) of 18 patients had 3 or more metastatic nodes.

Tumor extension to adjacent organs was detected in 15 (60%) of 25 cases (Table 2); extension was unknown in 1 case (4%). The site to which the tumor most frequently extended was the recurrent laryngeal nerve (12/24 [50%]), followed by the trachea (9/24 [38%]) and the esophagus (4/24 [17%]). Other sites to which the tumor extended are listed in Table 2. These sites were resected to achieve curative surgery.

Prognosis for Patients With ITET/CASTLE

Of 22 patients with ITET/CASTLE who underwent curative surgery, 7 (32%) had recurrence: 4 in distant organs, 2 locoregional, and distant and locoregional in 1. Distant organs showing recurrence were the lung (3 cases), liver (2 cases), bone (2 cases), mediastinum (1 case), and pleura (1 case).

Table 1

Surgical Procedures in 25 Cases of Intrathyroidal Epithelial Thymoma/Carcinoma Showing Thymus-like Differentiation

<table>
<thead>
<tr>
<th>Procedure</th>
<th>No. (%) of Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thyroidectomy</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>6 (24)</td>
</tr>
<tr>
<td>Subtotal</td>
<td>9 (36)</td>
</tr>
<tr>
<td>Lobectomy</td>
<td>8 (32)</td>
</tr>
<tr>
<td>Partial lobectomy</td>
<td>2 (8)</td>
</tr>
<tr>
<td>Lymph node dissection</td>
<td></td>
</tr>
<tr>
<td>Modified radical neck dissection</td>
<td>14 (56)</td>
</tr>
<tr>
<td>Central node dissection</td>
<td>4 (16)</td>
</tr>
<tr>
<td>Not done</td>
<td>6 (24)</td>
</tr>
<tr>
<td>Unknown</td>
<td>1 (4)</td>
</tr>
</tbody>
</table>
Locoregional recurrence included cervical lymph nodes (1 case), muscle (1 case), and local recurrence (2 cases).

Of the 22 patients who underwent surgery, postoperative radiation was performed as adjuvant therapy in 10 patients (45%); for 1 patient (5%), the receipt of postoperative radiation was unknown. Patients having tumors showing extension to adjacent organs underwent radiation therapy more frequently (P = .0062). Table 3 shows the relationships between adjuvant radiation therapy and extrathyroidal extension for 22 patients who underwent curative surgery. Of the 10 patients who underwent radiation therapy, 4 (40%) had recurrence, all in distant organs only, where radiation was not used. Of 11 patients who did not receive radiation therapy, 3 (27%) had recurrence; 2 (18%) had locoregional recurrence, and 1 (9%) had locoregional and distant recurrence.

Figure 1 shows the Kaplan-Meier curve for cause-specific survival (CSS) in patients with intrathyroidal epithelial thymoma/carcinoma showing thymus-like differentiation. The 5- and 10-year CSS rates were 90% and 82%, respectively. The CSS curves for patients with ITET/CASTLE with and without lymph node metastasis are shown in Figure 2, and those of patients with and without tumor extension to adjacent organs are shown in Figure 3. The 5- and 10-year CSS rates in patients without nodal metastasis were both 100%, whereas the rates in patients with nodal metastasis were 76% and 57%, respectively. Furthermore, none of the patients without extension to adjacent organs died of ITET/CASTLE, but the absence of nodal metastasis and tumor extension is considered an indicator of a favorable prognosis in ITET/CASTLE.

Discussion

We studied the clinicopathologic features, including predictors of prognosis, in 25 cases of ITET/CASTLE. This is the first study of this entity describing such a large number of cases. Although ITET/CASTLE histologically resembles SCC, the clinical outcomes for patients with ITET/CASTLE are much better than for patients with SCC. Therefore, accurate diagnosis is required. To establish the diagnosis, careful morphologic examination of H&E-stained sections is most important. ITET/CASTLE shares typical morphologic characteristics with certain types of thymomas, such as the following: (1) pleomorphic or spindle-shaped cells with oval nuclei having well-defined nucleoli, (2) well-bounded cell nests, and (3) peritumoral and intratumoral infiltration of lymphocytes and plasma cells.
In the present study, various markers were investigated that may have an accessory role in establishing the diagnosis. Because thyroglobulin and TTF-1 are markers of thyroid follicular cells, it is reasonable that all cases of ITET/CASTLE were negative for them. These markers, however, were also negative in all cases of carcinoma showing squamoid differentiation with or without undifferentiated component.

Previous studies indicated that CD5 is useful for diagnosing ITET/CASTLE because it is a marker for carcinoma of thymic origin. However, not all thymic carcinomas expressed CD5. Dorfman et al \(^6\) showed that 4 of 20 thymic carcinomas were CD5–, and, according to Berezowski et al \(^5\), 5 of 9 thymic carcinomas were CD5–. Indeed, in the present series, 14 of 17 ITET/CASTLE cases expressed CD5, but the remaining 3 were negative. Furthermore, the antibody for CD5 requires delicate immunohistochemical staining, and the staining results are not reliable for specimens with poor fixation. Indeed, in the present series, the immunohistochemical results could not be evaluated in 6 cases. Because none of the cases diagnosed as carcinoma showing squamoid features with or without anaplastic component were CD5+, CD5 can be a useful marker for diagnosing ITET/CASTLE. However, the lack of CD5 expression does not completely rule out ITET/CASTLE. The final diagnosis should be based on the H&E findings as described herein.

It is difficult to diagnose ITET/CASTLE preoperatively because clinical findings such as palpitation of hard tumors with poor mobility and frequent tumor extension to adjacent organs are features common in aggressive and advanced thyroid carcinomas. However, FNAB findings differing from those of typical thyroid carcinoma can be a clue to consider the possibility of ITET/CASTLE. Although only 1 case was diagnosed correctly by FNAB, the remaining cases showed unusual cytologic features not typical for papillary, follicular, medullary, and undifferentiated carcinoma. Some features typical for ITET/CASTLE, such as location in the lower part of the thyroid, lobulated pattern shown by ultrasonography, lack of calcification, lack of foci of other thyroid carcinomas, and lack of rapid tumor enlargement may also indicate that surgeons should suspect this disease, although none of these are specific for ITET/CASTLE.

Roka et al \(^8\) showed in their systematic literature review that node-negative ITET/CASTLE had a low risk of recurrence. In the present study, we demonstrated that none of the patients with node-negative tumors died of the disease, whereas the 5- and 10-year CSS rates for node-positive patients were 76% and 57%, respectively, indicating that nodal metastasis drastically affects survival. Similarly, patients without tumor extension to adjacent organs have not died of the disease. These findings strongly suggest that these 2 features are significant prognostic factors of ITET/CASTLE.

In our series, the incidence of tumor extension to adjacent organs and nodal metastasis were high, at 60% and 50%, respectively. However, locoregional recurrence was observed in only 3 (14%) of 22 patients who underwent curative surgery, suggesting that surgeons should make a maximal effort to curatively resect the tumor, including resection of adjacent organs to which tumors extend. Furthermore, although the number of metastatic nodes is usually small, 29% of patients (5/17) showed nodal metastasis in the lateral compartment.
Thus, it may be better to perform modified radical neck dissection not only therapeutically but also prophylactically.

Miyauchi et al\(^1\) suggested the possible effect of radiation therapy for ITET/CASTLE in their original article because this neoplasm shared some features with thymic carcinoma. Roka et al\(^8\) also described the usefulness of radiation as an adjuvant therapy in their review article. In the present series, patients with tumor extension to adjacent organs underwent postoperative radiation more frequently, possibly because surgeons have regarded such tumors as biologically aggressive and predicted that they are likely to recur. This can explain why the recurrence rate of patients with radiation therapy (40%) was even higher than that of patients without radiation (27%) in the present series. It is interesting that of 11 patients without radiation therapy, 3 had locoregional recurrence, whereas patients with radiation therapy had recurrence only in distant organs not covered by radiation. It is therefore suggested that, although tumor extension and nodal metastasis are rather common events in this disease, curative surgery, including resection of organs to which the tumor has extended, and systematic lymph node dissection followed by radiation therapy can prevent locoregional recurrence.

We demonstrated that patients with ITET/CASTLE have a good prognosis if the tumor is resected competently. Although it is difficult to diagnose ITET/CASTLE preoperatively, FNAB findings could be a clue to the diagnosis. Clinical features such as tumor location at the lower part of the thyroid, lobulated tumor, lack of calcification, lack of rapid tumor growth, and lack of foci of other thyroid carcinomas may also help surgeons consider the possibility of this disease preoperatively. Curative surgery followed by radiation therapy seems to be important to prevent locoregional recurrence and should contribute to a better outcome for patients with ITET/CASTLE.

References


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