Squamous Cell Carcinoma of Thyroid: possible thymic origin, so-called ITET/CASTLE
History of ITET/CASTLE

First Report: Gross Appearance and Prognosis

Kaplan-Meier curves for cause specific survival in 3 groups

Cummurative survival(%)
First Report: Gross Appearance and Prognosis

First Autopsy Report:
Carcinoma of Possible Thymic Origin Presenting as a Thyroid Mass: A New Subgroup of Squamous Cell Carcinoma of the Thyroid

KENNICHI KAKUDO, MD, ICCHI MORI, MD, NOKIATSU TANAKA, MD, AND KICHI WATANABE, MD

From the Department of Pathology, Tokai University School of Medicine, Isehara, Japan

Introduction
So-called intrathyroidal thymoma (ITT) is a relatively new entity separate from squamous cell carcinoma of the thyroid [Hasagawa et al., 1985; Miyazaki et al., 1985]. It has been reported as a benign or low-grade malignant tumor that survived more than 10 years after surgical treatment. Therefore, it must be distinguished from squamous cell carcinomas of the thyroid which are just as aggressive as undifferentiated (anaplastic) carcinomas of the thyroid [Carrasquillo et al., 1985; Goldman, 1964; Huang and Assor, 1971; Meissner and Warren, 1990; Nishiyama et al., 1972; Rosai et al., 1985; Shinoda and Tsukada, 1980]. ITT presents characteristic features distinguishable from squamous cell carcinoma of the thyroid. It shows expansile growth, a lobular cut surface, rare mitoses, and lymphocytic infiltration, while squamous cell carcinoma of the thyroid exhibits invasive growth, frequent mitoses, necrosis, granulocytic infiltration, and a coexisting tumor [Carrasquillo et al., 1985; Huang and Assor, 1971; Nishiyama et al., 1972; Rosai et al., 1985; Shinoda and Tsukada, 1980].

Key Words: thyroid gland, thyroid neoplasms, thymus, epithelial thymoma, T lymphocytes

Case Report
A 59-year-old man noticed a lump on the left side of his neck and visited Tokai University Hospital. The mass was localized in the left lobe of the thyroid, extending to the left submandibular region. It was a cold nodule by technetium scintigraphy and was demonstrated as a hot nodule by iodine scintigraphy. Excision biopsy of a cervical lymph node: demonstrated metastatic epithelial malignancy and it was interpreted as a poorly differentiated squamous cell carcinoma. No primary tumor was found in the nasopharynx, larynx, esophagus, trachea, or lungs. A subtotal thyroidec"omy with modified radical neck dissection was performed in July 1984, which was followed by irradiation to the neck. The patient received 30 Gy, and there was no evidence of recurrence up to 5 years after surgery.

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Address reprint requests to: K. Kakudo, Department of Pathology, Tokai University School of Medicine, 259-11 Isehara, Japan.
Cervical thymic tissue nearby.

Hematogenous metastasis (lungs, bone and liver) was found in advanced stage of ITET/CASLE.
2240 肺転移
Ki-67, Tokai university autopsy No 2249

CD5
History of ITET/CASTLE

First Report: Gross Appearance and Prognosis


First Autopsy Report:


Proposal of Classification:


Classification of thyroid tumors of thymic differentiation in WHO classification, 2004

1) Extrathyroid tumor
   1. Ectopic hamartomatous thymoma

2) Intrathyroid tumor
   1. Ectopic thymoma
   2. Carcinoma showing thymus-like differentiation (CASTLE)
   3. Spindle cell tumor with thymus-like differentiation (SETTLE)

Synonyms: intrathyroid epithelial thymoma by Miyauchi, primary thyroid thymoma by Asa, carcinoma showing thymus-like differentiation by Chan and lymphoepithelioma-like carcinoma by Sheck.
My lecture is based on 15 cases of Intrathyroidal Epithelial Thymoma (ITET) / Carcinoma Showing Thymus-Like Differentiation (CASTLE) from consultation files and personal experience.
Overall survival analysis of 14 cases of ITET

Kaplan-Meier method

This indolent nature is different from primary squamous cell carcinoma.
The cumulative survival rate of all 38 patients, those patients with complete resection and those with incomplete resection by Kaplan-Meier analysis.
Clinical summary of the 15 cases

The average age was 49.9(25-73) years old.

Male/Female ratio was 7:8.

The average tumor size at surgery was 4.2cm.

Lymph node metastasis at surgery was 40%.

The incidence in Japan was 0.083%, which was estimated from 8 cases out of 9582 carcinomas.
**Gross Appearance**

1. Solid tumor with lobulation
2. Pushing margin and No capsule
3. No necrosis, calcification or cystic change
4. Grey white or ivory white
5. Cervical thymus may be found near by
Histological Characteristics

1. Expansive growth
2. No capsule
3. Solid growth
4. Keratinization and squamous cell differentiation
5. Lymphocytes in tumor nests and stroma
6. Cytologically, ill defined cell border
1 Expansive growth
2 No capsule
3 Solid growth
It is an invasive carcinoma!
**Mediastinal Thymic Carcinomas**

Histologic Subtypes in WHO Classification

1. Squamous cell carcinoma type
2. Basaloid carcinoma type
3. Lymphoepithelioma-like type
4. Sarcomatoid (carcinosarcoma) type
5. Clear cell type
6. Adenocarcinoma type
7. Mucoepidermoid type
8. Neuroendocrine carcinoma (carcinoid)
9. Undifferentiated thymic carcinoma
Histological Types of ITET/CASTLE

1: Squamous cell carcinoma
2: Lymphoepithelioma-like carcinoma
3: Neuroendocrine carcinoma
ITET was identified in UC or SCC group.
Keratinization and squamous cell differentiation
Lymphoepithelioma of the thyroid is a synonym.

5 Lymphocytes in tumor nests and stroma
6 Cytologically ill defined cell border
16-1500, Neuroendocrine carcinoma type
Neuroendocrine carcinoma

NSE

synaptophysin
Berezowski et al and Dorfman et al reported that ITET/CASTLE and thymic carcinoma were positive for CD5.
Dorfman et al reported that antiapoptosis protooncogenes (bcl-2 and mcl-1) were expressed in all 5 cases of ITET/CASTLE.
Reinmann et al reported that all 11 cases of ITET/CASTLE exhibited positive staining for p63, HMWK, CEA and CD5.
CD5 is a membrane bound protein and a member of scavenger receptor cysteine-rich superfamily. In humans, the gene is located on the long arm of chromosome 11. T cells express higher levels of CD5 than B cells. In the thymus, both epithelium and lymphocyte express CD5 and there is a correlation with CD5 expression and strength of the interaction of the T cell towards self-peptides.

1. Positive in most of T cell neoplasmas, mediastinal thymoma and thymic carcinoma
2. Negative in most of the other carcinomas
16-1500, Intrathyroidal epithelial thymoma
AE1/AE3(+)，thyroglobulin(-)
Immunohistochemical profiles of ITET/CASTLE

Positive: CD5, High molecular weight keratin p63, p53, bcl-2, mcl-1

Negative: Thyroglobulin, TTF-1, Calcitonin, CGRP, CEA
Differential Diagnosis

1: Squamous cell carcinoma of thyroid
   CD5 - , high MIB-1 index (>30%),
   high mitotic figures, invasive pattern
2: Undifferentiated carcinoma
   CD5 - , high MIB-1 index (>30%),
   high mitotic figures, necrosis +, granulocyte infiltration
3: Medullary (C cell) carcinoma
   CD5 - , calcitonin +, amyloid +, lymphoid stroma -
4: Solid carcinoma of follicular cell origin
   (insular carcinoma, poorly differentiated carcinoma)
   CD5 - , thyroglobulin +, keratinization -
Electron microscopic study was applied on 2 cases of ITET (lymphoepithelioma type).
Etiological consideration of ITET/CASTLE

EB virus was not detected in ITET/CASTLE


In situ hybridization for EBV DNA was applied in 2 cases but they were negatively labelled, usually it is positive in lymphoepithelioma of upper aerodigestive tract.
Histogenesis of ITET/CASTLE: Ectopic Tissue and Embryonic Remnant (胸腺、鳃囊、solid cell nest) are suggested.
Branchial pouch (solid cell nest) a possible origin for ITET/CASTLE, because thymic epithel and solid cell nests are positive for CD5 and p63.

Thank you for joining this lecture!

和歌山城(Wakayama CASTLE)