

Case Report

Intrathyroid thymic carcinoma: report of two cases with pathologic and immunohistochemical studies

Yan-Hua Sun^{1*}, Juan Xu^{2*}, Ming Li³

¹Department of Pathology, Shenzhen Second People's Hospital, Sun Yat-sen University, Shenzhen, Guangdong Province, PR China; ²Department of Pharmacology and Proteomics Center, Zhongshan School of Medicine, Sun Yat-sen University, Guangzhou, Guangdong Province, PR China; ³Department of Immunology, College of Basic Medical Science, Central South University, Changsha, Hunan, PR China. *Equal contributors.

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Abstract: Intrathyroid thymic carcinoma (ITCA) is a rare neoplasm of the thyroid gland, that is difficult to diagnose because of its complex pathologic and immunohistochemical characteristics. Here, we report two cases that may provide a better understanding of this disease. Case 1 is a 30-year-old man, and Case 2 is a 42-year-old man. The two cases showed an irregular solid thyroid mass on sonography. Histological examination revealed the solid growth of epithelial cells separated by bands of dense, hyalinized, and fibrous stroma. Tumor cells were positive for the expression of CD5, HMWK, CK19, CK5/6, CK7, EMA, CD117, p63, Bcl-2, and NANOG. It is noteworthy that the neuroendocrine markers Syn, NSE, and CgA were also observed. In Case 1, chemotherapy combined with radiotherapy, chest CT showed lung metastasis 4 months after resection. The patient was alive as of postoperative follow up lasting 46 months. Radical operation combined with radiotherapy was performed in case 2, and the patient was alive as of follow-up lasting 42 months.

Keywords: Thyroid neoplasm, histopathology, pathologic diagnosis, neuroendocrine markers

Introduction

Intrathyroid thymic carcinoma (ITCA) is a rare malignant tumor of the thyroid gland. A few cases have also occurred in the soft tissue of the neck. ITCA typically occurs in adults in the fifth decade, and shows no significant sexual or racial predominance. Histologically, it is similar to thymic squamous cell carcinoma [1]. According to the tumor classification system published by the World Health Organization 2017, the tumor previously known as 'carcinoma showing thymus-like differentiation of the thyroid (CASTLE)' is termed 'intrathyroid thymic carcinoma'. Intrathyroid thymic carcinoma is synonymous with intrathyroid epithelial thymoma, primary thyroid thymoma, and lymphoepithelioma-like carcinoma of the thyroid gland as an independent clinicopathological entity of thyroid tumors. The expression of common protein markers such as CD5, CK, CD117, and p63, Bcl-2, and NANOG help ITCA to distinguish from other tumors. It has also been reported that CASTLE has immunohistochemical fea-

tures of neuroendocrine differentiation, such as synaptophysin (Syn) and chromogranin A (CgA) [2, 3]. To date, neuroendocrine differentiation in ITCA has not been described in detail. In our two cases, in addition to strong positive expression of Syn, and CgA in tumor cells, another neuroendocrine marker, neuron-specific enolase (NSE), is also expressed. Moreover, one of the cases is a 30-year-old man, making ITCA hard to diagnose. Although it is generally thought that ITCA has a lower degree of malignancy than thyroid carcinoma, it can progress and even lead to death.

Case presentation

Case 1, a 30-year-old man, had a painless mass in the neck, which had recently rapidly increased in size and was accompanied by hoarseness and dysphagia that lasted approximately 1 year. Physical examination showed a hard, 5 cm mass in the right side of the neck. No cervical lymph nodes were palpable. Thyroid function and calcitonin values were within nor-

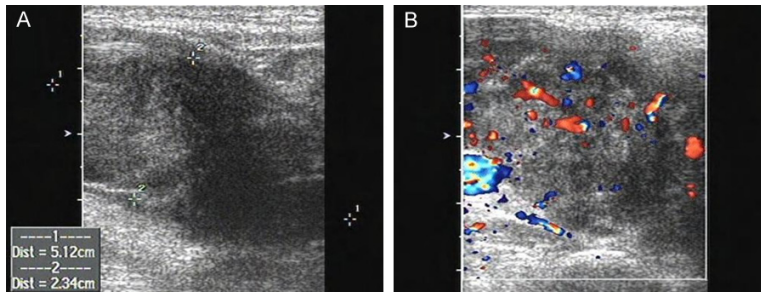


Figure 1. Sonography revealed a solid, lobulated hypoechoic mass with heterogeneous internal echoes in the right lower thyroid in case 1 (A). The tumor showed moderate vascularity on color flow images and showed no evidence of calcification (B).

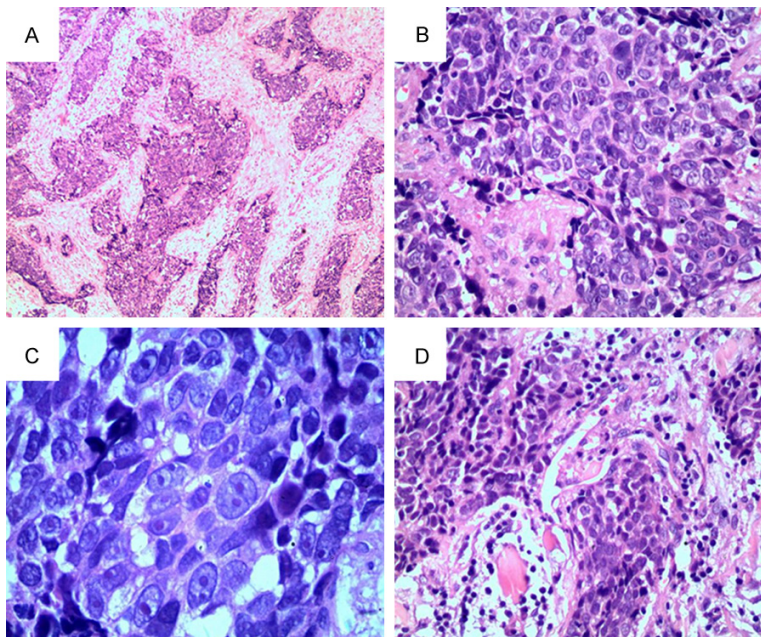


Figure 2. Histological examination disclosed a solid growth of epithelial cells that were separated by bands of dense, hyalinized, and fibrous stroma (H&E, 40 \times) (A). The polygonal-shaped or spindle-shaped tumor cells contained pale or abundant eosinophilic cytoplasm (H&E, 100 \times) (B). A large vesicular nucleus, and prominent nucleoli (H&E, 400 \times) (C). There were infiltrations of small lymphocytes and plasma cells in the tumor and fibrous stroma (H&E, 200 \times) (D).

mal limits. Nasopharyngolaryngoscopy examination confirmed palsy of the right vocal cord. Sonography revealed a 5.1 cm \times 2.3 cm hypoechoic and heterogeneous irregular solid mass located at the lower pole of the right thyroid (**Figure 1A**). The tumor had moderate vascularity on color flow images and showed no evidence of calcification (**Figure 1B**). The muscles of the neck, the trachea, and the right laryngeal nerve were invaded. Magnetic resonance imaging (MRI) showed that the tumor had metastasized to the mediastinal lymph

nodes. After palliative surgery, chemotherapy combined with 60 Gy/30 radiotherapy was administered for 47 days. The tumor shrank significantly after six cycles of chemotherapy with docetaxel and cisplatin. Chest computed tomography (CT) taken 4 months after resection showed well-defined nodules of 0.6 cm in diameter. The patient was still living at 46 month post-operative follow-up.

Case 2, a 42-year-old, man had a painless mass on the side of the thyroid accompanied by hoarseness. Physical examination revealed a hard, 4 cm mass in the left side of the neck and enlarged neck lymph nodes. Thyroid function and calcitonin values were within normal limits. Nasopharynx olaryngoscope examination confirmed palsy of the left vocal cord. Sonography revealed a 4.0 cm \times 3.0 cm irregular solid mass on the left thyroid. The tumor had moderate vascularity on color flow images, and showed evidence of calcification. Radical operation and radiotherapy were performed. The patient was still living at the 42-month post-operative follow-up. Written informed consent was obtained from both patients for publication of the case reports and any accompanying images.

Gross observation showed that the specimen in Case 1 was an aggregate of pale pink fragments of moderate or soft consistency and was 4 cm \times 4 cm \times 1.5 cm in size. In Case 2, the specimen was a grayish-white, solid, with lobulated margins and was 3.8 cm \times 3.0 cm \times 3.0 cm in size. Histologic examination showed solid growth of epithelial cells separated by bands of dense, hyalinized, and fibrous stroma (**Figure 2A**). The polygonal and spindle-shaped tumor cells with ill-defined cell borders were arranged in nests, sheets, islands, and cords. The tumor

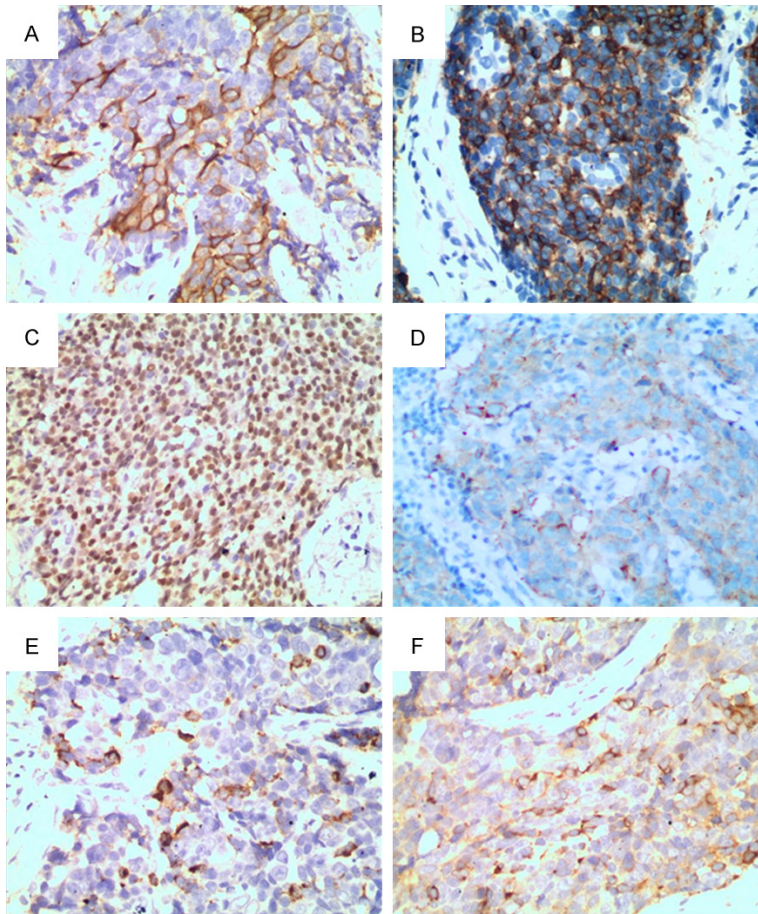


Figure 3. The tumor cell membrane was positive for CD5 (A) and CD117 (B). Diffuse positivity for p63 was observed (C). The tumor cells displayed diffuse cytoplasmic staining for NANOG (D). CgA was positive in scattered clusters of tumor cells (E) and Syn showed diffuse positivity (F).

cells contained pale or abundant eosinophilic cytoplasm (**Figure 2B**), a large vesicular nucleus, and prominent nucleoli (**Figure 2C**). There were infiltrations of plasma cells, small lymphocytes, and fibrous stroma in the tumor (**Figure 2D**), and moderate mitoses and slight necrosis. Case 2 showed diffuse Hassall's corpuscle-like structures and clear keratinization. There was extensive extrathyroidal extension. No perineural or vascular invasion was seen, and paratracheal lymph nodes were uninvolved. Immunohistochemistry (IHC) showed positive expression of cluster of differentiation 5 (CD5), which was mainly expressed on the cytomembrane (**Figure 3A**). Diffuse positivity was observed for human creatinine kinase (CK) (pan), high-molecular weight kininogen (HMWK), CK19, CK5/6, CK7, epithelial membrane antigen (EMA), CD117 (**Figure 3B**), p63 (**Figure 3C**), B-cell lymphoma 2 (Bcl-2), and non-processed pseudooncogene (NANOG) (**Figure 3D**) was

observed. Tumor cells displayed multifocal cytoplasmic staining for carcinoembryonic antigen (CEA), and were negative for CK20, thyroglobulin, thyroid transcription factor (TTF-1), vimentin, and calcitonin. CgA showed positivity in the scattered clusters of tumor cells (**Figure 3E**) and Synaptophysin (Syn) and NSE showed diffuse positivity (**Figure 3F**). Cells were negative for CD56. Lymphocytes were positive for T-cell markers and negative for B-cell markers. All the clinical data were obtained and tissue analyses were handled with care and respect to protect both patients' anonymity. This study was approved by the ethics committees of the Shenzhen Second People's Hospital.

Discussion

ITCA originates from ectopic thymic tissue in the thyroid solid cell nests (SCNs), and it retains the potential for differentiation from thymic tissue [4, 5]. ITCA usually occurs in the thyroid or soft tissue of the neck [5, 6]. The micro-

scopic appearance of ITCA makes it indistinguishable from thymic carcinoma, and it is histologically similar to mediastinal thymic carcinoma. Evidence for the thymus rather than thyroidal origin of CASTLE was provided by its immunoreactivity for CD5, CD117, HCK, Bcl-2, and p63 (all of these markers being usually positive in thymic carcinoma) and it was negative for thyroglobulin and TTF-1. It tends to have regional lymph node metastasis and local recurrence, but its behavior is somewhat indolent, more so than that of undifferentiated thyroid carcinoma. However, indolent tumors occasionally take an aggressive course [6]. The recurrence time of CASTLE ranges from 3 months [7] to 17 years [4, 8] after surgery. Thus, regular postoperative follow up is important for the early detection of recurrence and metastasis. In our case, the patient had mediastinal lymph node metastasis at the time of diagnosis of ITCA, and lung metastasis

appeared 4 months after resection. Chest CT showed well-defined nodules in the right lung. The tumor can spread extensively into the trachea, esophagus, muscles, connective tissue, skin, jugular vein, vagus and mediastinum [2]. Sonography showed that the solid mass had a lobulated outline, hypoechoic echo pattern, and moderate vascularity. The CT scan showed soft-tissue density, no calcification, and slight enhancement upon treatment with contrast agent. The mass was isointense on T1-weighted examination, enhanced moderately with a central area treated with contrast agents, and was hyperintense in T2-weighted images [9].

Histologically, ITCA was difficult to distinguish from the epithelium of thyroid follicles, especially undifferentiated carcinoma. CD5 expression was detectable in ITCA, with a predominantly membranous pattern, but was not detectable in undifferentiated carcinoma. CD5 is an important marker of the pathologic diagnosis of ITCA. The sensitivity of CD5 is 82% [10] and the specificity is 100% [11]. Microscopically, the epithelioid tumor cells showed island-like and nested-like distribution, infiltration, or were interspersed between the thyroid follicles. The IHC markers particularly used for their identification were CD21 and CD35. The immunoreactivity of CD5, CEA, p63, and HMWK could be used to distinguish CASTLE from other thyroid neoplasms [5], whereas the four markers were consistently negative in follicular carcinoma, poorly differentiated carcinomas, and follicular adenoma. The expression of neuroendocrine markers in thymic carcinoma is positive. To date, neuroendocrine differentiation in ITCA has not been described in detail. In our case, the tumor cells showed strong positivity for neuroendocrine markers, Syn, NSE, and CgA. It will be an important indicator of thymic differentiation of ITCA. The tumor showed positive expression of CD5 and CD117, which can facilitate the discernment of ITCA from histologically similar conditions including lymphoepithelial carcinoma, neuroendocrine carcinoma, poorly differentiated squamous cell carcinoma, malignant melanoma and metastatic carcinoma. Veits and colleagues tested the sequence underlying the pathogenesis of CASTLE using CGH. The CGH data indicated that CASTLE has sequence and chromosomal imbalances similar to those of thymomas and thymic carcinomas [12].

Surgical excision is the best therapeutic option for ITCA. Because local recurrence and lymph nodes involvement are common, postoperative radiotherapy is usually used to reduce the recurrence rate in ITCA. Systematic adjuvant radiotherapy is recommended for ITCA because of its radiosensitivity. Tumors disappeared from one patient who was treated by radiotherapy alone, and CT did not show local recurrence at least 7 years [13]. There are few reports of the effectiveness of chemotherapy and radiotherapy in combination. Chemotherapeutic agents including cisplatin, liposomal doxorubicin, epirubicin, docetaxel, gemcitabine, and irinotecan have been tried in some patients [14]. Chow et al. reported three cases of CASTLE [15]. They observed that patients with CASTLE had a good clinical outcome after chemotherapy followed by external radiation therapy. Etoposide and carboplatin are effective in chemoradiotherapy, and chemotherapy of docetaxel and cisplatin can effect complete remission of CASTLE lung metastasis. However, one patient showed lung metastasis after treatment with chemotherapy of docetaxel and cisplatin combined with radiotherapy after palliative surgery. Although the tumors significantly shrank in our case, this may be because of individual differences or tumor heterogeneity.

Conclusions

In summary, the diagnosis of ITCA is challenging, especially among young adults. We reported two cases of ITCA. ITCA has a complex histomorphology. Although protein markers can be used to facilitate diagnosis and differential diagnosis, individual differences remain between each case. These samples showed expression of common protein markers such as CD5, CK, CD117, and p63, Bcl-2, and NANOG and also the neuroendocrine markers Syn, NSE, and CgA. These results expand our knowledge of ITCA. Currently, there is no definitive treatment regimen for this disease, so treatment of patients with ITCA should be planned on a case-by-case basis.

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Disclosure of conflict of interest

None.

Address correspondence to: Ming Li, Department of Immunology, College of Basic Medical Science, Central South University, Changsha 410078, Hunan, PR China. Tel: 086-731-82355010; Fax: 086-731-84470589; E-mail: liming@csu.edu.cn; Juan Xu, Department of Pharmacology and Proteomics Center, Zhongshan School of Medicine, Sun Yat-sen University, Guangzhou, Guangdong Province, PR China. E-mail: hillyxj@sina.com

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