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Case Report

Clinical Analysis of Thyroid Carcinoma Showing Thymus-Like Differentiation: Report of 8 Cases

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Thyroid carcinoma showing thymus-like differentiation (CASTLE) is a kind of rare neoplasm of the thyroid gland. Because thyroid CASTLE is rare and difficult to diagnose, its clinicopathologic features have not been well defined, and no universally accepted treatment recommendation is available. We analyzed retrospectively the clinicopathologic data of 8 patients with thyroid CASTLE who underwent surgery and radiotherapy at the Shengjing Hospital of China Medical University between December 2008 and June 2012. All patients accepted radical surgery. All patients accepted postoperative radiotherapy, except one 79-year-old patient. There was no evidence of recurrence or metastasis during the follow-up period. The pattern of immunohistochemical staining was similar to that of thymic carcinoma. Six of 8 CASTLE cases expressed CD5. All 8 CASTLE patients were negatively expressed in thyroglobulin, thyroid transcription factor 1, and calcitonin. Patients with thyroid CASTLE have good outcomes after radical resection and postoperative radiotherapy. Positive CD5 immunoreactivity can contribute to diagnosis of this disease.

Key words: CASTLE – Thyroid neoplasms – CD5 – Thymus

Thyroid carcinoma showing thymus-like differentiation (CASTLE) is a kind of rare neoplasm arising from the thyroid gland, which bears histologic and immunophenotypic resemblance to thymic carcinoma. It was originally described as intrathyroidal epithelial thymoma by Miyauchi *et al* in 1985.[1] In 2004, this disease was designated as an independent clinicopathologic entity among thyroid carcinomas according to the World Health Organization classification of tumors of endocrine organs.[2] Thyroid CASTLE may arise from an ectopic thymus or branchial pouch remnants in the thyroid gland, which retain the capability of thymic differentiation.[3] Histologically, thyroid CASTLE resembles

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squamous cell carcinoma and anaplastic carcinoma of thyroid. Distinguishing thyroid CASTLE from these aggressive neoplasms is important, because thyroid CASTLE has a comparatively favorable prognosis with indolent clinical course.[3–6]

Since thyroid CASTLE is rare and difficult to diagnose, its clinicopathologic features have not been well defined, and no universally accepted treatment recommendation is available. In this study, we retrospectively studied the clinicopathologic data of 8 cases of thyroid CASTLE diagnosed in Shengjing Hospital of China Medical University. We analyzed the clinicopathologic features, diagnosis, and treatment of thyroid CASTLE in these cases combined with a review of the literature.

Materials and Methods

Clinical data

Clinicopathologic data of 8 surgically resected specimens of thyroid CASTLE were available at Shengjing Hospital of China Medical University between December 2008 and June 2012. The specimens were from 5 male and 3 female patients, ranging in age from 32 to 79 years (mean ± SD, 56 ± 16 years). All hematoxylin and eosin (H&E)–stained sections were independently reviewed by 2 experienced pathologists to confirm the diagnosis. Clinical characteristics, treatment, and outcome of patients are showed in Table 1. Preoperative laboratory findings, cervical ultrasonographic (US) and computed tomographic (CT) features were evaluated.

Treatment

All patients underwent radical surgery for their tumors (Table 1). All patients accepted postoperative radiotherapy, except one 79-year-old patient. External radiotherapy encompassed the thyroid bed and cervical lymph node area. One case with superior mediastinal lymph node metastasis received superior mediastinal radiotherapy.

Follow-up

All patients were followed postoperatively for 2 to 45 months (median time, 12 months). No recurrence or metastasis was found in any patient during the follow-up period.

Results

Clinical features and imaging findings

The clinical characteristics of the patients are shown in Table 1. The main complaint of all patients was a painless, slow-growing cervical mass. The mean size of the lesions was 4 cm (range, 2–6 cm). Hoarseness due to recurrent laryngeal nerve (RLN) paralysis was found in 2 patients. None of the patients complained of dyspnea and dysphagia. The serum concentrations of thyroxine, thyrotropin, antithyroid peroxidase antibody, antithyroglobulin antibody, and thyroglobulin in all patients were normal. Three patients had tumors confined to the thyroid gland, and 5 had perithyroidal tissue infiltration. Cervical US commonly revealed a solid, hypoechoic mass without calcification but with moderate vascularity (Fig. 1). The lesions commonly exhibited soft tissue density with unclear border, but without calcification on nonenhanced CT. On a contrast-enhanced CT, the corresponding lesion appears slightly enhanced (Fig. 2). When the mass was great, CT showed that the mass involved the superior mediastinum and compressed the trachea (Fig. 3).

Pathologic features

Macroscopically, the tumors presented unclear border, grayish white in color, hard in texture. Microscopically, the tumors were usually composed of variably sized epithelial cell nests separated by dense fibrous septa with many lymphocytes and plasma cell infiltration (Fig. 4A and 4B). Tumor cells contained eosinophilic cytoplasm and vesicular nuclei with distinct nucleoli. There was no histologic finding that suggested typical thyroid tumor, including papillary carcinoma, follicular carcinoma, and medullary carcinoma.

Immunohistochemically, the tumor cells were positively immunoreactive for CD5 in 6 cases (Fig. 4C), p63 in 2 cases, and cytokeratin in 2 cases. The tumor cells were negative for thyroglobulin, TTF-1, and calcitonin.

Discussion

Thyroid CASTLE is a kind of rare neoplasm arising from the thyroid gland. Besides thyroid, CASTLE also occurs in the left parapharyngeal space,[5] carotid and posterior space,[7] and subcutaneous tissue of head and neck.[8] This tumor occurs in middle-aged individuals with a mean age of 50 years and has a slight female predominance (female to male ratio,

Table 1 Clinical characteristics, treatment, and outcome of patients with CASTLE

Patient No.	Age/ sex	Tumor location/size (cm)	Lymph node metastasis	Invasion	Operation	Postoperative radiotherapy	Follow-up (mo)	Outcome
1	32/F	Lower pole of right lobe/2 cm	Negative	Strap muscle	Right lobectomy, right strap muscle resection, right selective neck dissection	50 Gy	2	Alive with NED
2	62/M	Lower pole of left lobe/5 cm	Positive	Strap muscle, left internal jugular vein, left RLN	Left lobectomy, left strap muscle resection, left internal jugular vein and RLN resection, bilateral modified neck dissection	60 Gy	4	Alive with NED
3	62/F	Left lobe, isthmus/5 cm	Positive	Left internal jugular vein, left RLN	Total thyroidectomy, left internal jugular vein and RLN resection, bilateral modified neck dissection	60 Gy	4	Alive with NED
4	45/M	Left lobe/5 cm	Positive	Strap muscle	Left lobectomy, left strap muscle resection, left modified neck dissection	56 Gy	12	Alive with NED
5	40/F	Lower pole of right lobe/4 cm	Positive	Strap muscle	Right lobectomy, right strap muscle resection, right modified neck dissection	56 Gy	12	Alive with NED
6	79/M	Lower pole of right lobe/5 cm, upper pole of left lobe/3 cm	Negative	Negative	Total thyroidectomy, central compartment dissection	No	15	Alive with NED
7	52/M	Lower pole of right lobe/4 cm	Negative	Negative	Right lobectomy, right selective neck dissection	50 Gy	27	Alive with NED
8	73/M	Lower pole of right lobe/6 cm	Positive	Negative	Right lobectomy, right modified neck dissection	56 Gy	45	Alive with NED

F, female; M, male; NED, no evidence of disease; RLN, recurrent laryngeal nerve.

1.3:1),[6,9] In our study, the mean age at initial diagnosis was 51 years, and the female to male ratio was 1:1.7. Because the number of cases was small, there seems to be no significant sexual predominance in our study. The general initial presentation is a painless, slow-growing cervical mass, which is consistent with previously published literature.[6]

Preoperative diagnosis of thyroid CASTLE is very difficult, because its clinical manifestations are commonly seen in other aggressive and advanced thyroid carcinomas in the following aspects: hard mass with poor mobility and invasion to adjacent organs. Furthermore, the images of thyroid CASTLE are not specific. US examination commonly reveals a solid, hypoechoic mass without calcification but with moderate vascularity. The nonenhanced CT commonly shows a soft tissue density with unclear border, but without calcification. On a contrast-enhanced CT, the corresponding lesion appears slightly enhanced. The value of fine needle aspiration biopsy (FNAB) in the preoperative diagnosis of thyroid CASTLE is limited.[5–7,10,11] However, the differences between FNAB findings

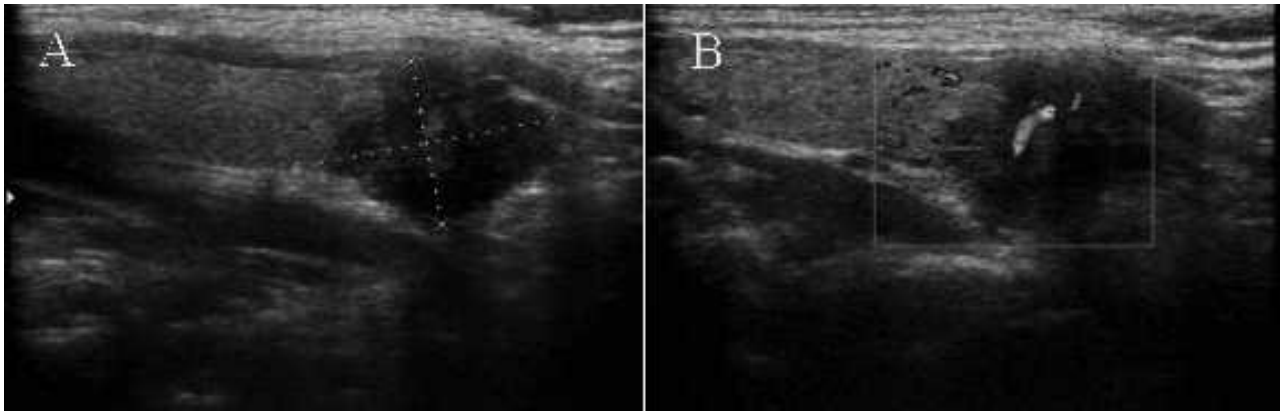

Fig. 1 (A) Thyroid US reveals a hypoechoic, noncalcified, solid mass. (B) Color flow Doppler US reveals moderate vascularity within the lesion.

and those of typical thyroid carcinoma can be a clue to consider the possibility of thyroid CASTLE.[12]

According to similarities in histology and immunophenotype between CASTLE and thymic carcinoma, thyroid CASTLE is believed to arise either from ectopic thymus or branchial pouch remnants in thyroid.[1,3,13] CASTLE has some typical morphologic characteristics in H&E-stained sections, such as pleomorphic or spindle-shaped cells, with oval or vesicular nuclei having prominent nucleoli, fibrous septa dividing the tumor nests, peritumoral and intratumoral infiltration of lymphocytes and plasma cells, infrequent mitoses, mild nuclear atypia, which are absent in papillary carcinoma, follicular carcinoma, medullary carcinoma, and undifferentiated carcinoma.[1,12,14,15]

Immunohistochemical studies can differentiate thyroid CASTLE from other malignant thyroid neoplasms. Similar to thymic carcinoma, thyroid CASTLE is immunohistochemically positive for CD5, but negative for calcitonin, thyroglobulin, and TTF-1. The majority of thymomas or other malignancies are CD5 negative.[4,10,16] It is reported that expression of high molecular weight keratin (HMWCK), carcinoembryonic antigen (CEA), and p63 in CASTLE are evidence of thymic origin and are useful diagnostic markers to distinguish thyroid CASTLE from other thyroid neoplasms.[13] Ito *et al* reported a sensitivity and a specificity of 82% and 100%, respectively, for CD5 positive for the diagnosis of CASTLE.[6] In our study, 6 of 8 CASTLE cases expressed CD5, and 2 of 8 cases expressed p63 and cytokeratin. All 8 CASTLE patients are negatively expressed for thyroglobulin, TTF-1, and calcitonin. Therefore, negative expression of CD5 does not completely rule out thyroid CASTLE according to our study. The final diagnosis of thyroid CASTLE should be based on the H&E findings as described herein. It is important to differentiate thyroid CASTLE from squamous cell carcinoma or anaplastic carcinoma of thyroid, because the latter 2 carcinomas have poor prognosis. In a recent report, the expression of S100A9, a marker of squamous cell origin, proved to be useful in discriminating CASTLE from squamous cell carcinoma or anaplastic thyroid carcinoma with squamoid component.[17]

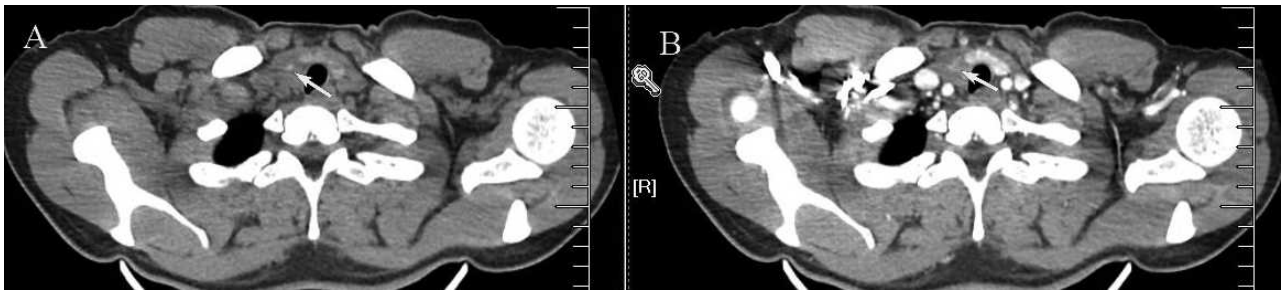

Fig. 2 (A) Nonenhanced CT shows a soft tissue density mass without calcification. (B) On a contrast-enhanced CT, the corresponding lesion appears slightly enhanced.

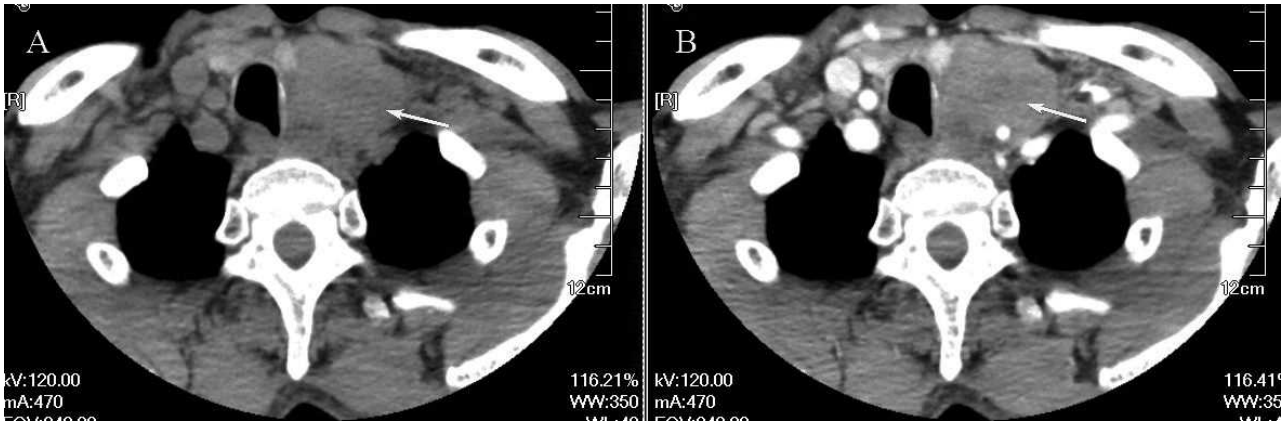

Fig. 3 (A) Nonenhanced CT shows an isodense mass located in the lower pole of the thyroid gland. The mass displaced the trachea to the right side and involves the superior mediastinum. (B) On a contrast-enhanced CT, the corresponding lesion appears slightly enhanced.

Because of the rarity of CASTLE, definitive management remains uncertain. Thyroid CASTLE is considered to be a low-grade malignant tumor with indolent biologic behavior and favorable prognosis. Generally, surgical resection is considered as the first therapeutic option. CASTLE often invades adjacent tissues and metastasizes to regional lymph nodes. In our study, the incidence of tumor extension to both adjacent organs and nodal metastasis was 62.5%. Ito *et al* reported that the incidence of regional organ invasion and nodal metastasis was 60% and 50%, respectively, and the incidence of lateral compartment metastasis was 27.8%. Therefore, thyroidectomy and neck dissection should always be performed.[6] We considered that radical resection should include thyroidectomy, resection of invaded adjacent organs, and neck dissection. Total thyroidectomy or thyroid lobectomy is indicated when the tumor involves the bilateral or unilateral thyroid gland. If the tumor extensively invades the adjacent organs, they should be resected too. When the tumor extensively invades the larynx, trachea, esophagus, or even the innominate vein, surgical procedures are challenging because reconstruction of the upper aerodigestive tract is needed.[9,18,19] Central compartment dissection is necessary for all thyroid CASTLE. And, suspected or proven lateral compartment cancer should receive selective neck dissection or modified neck dissection.[6,20]

Some of the literature has reported that postoperative radiation could prevent locoregional recurrence.[1,5,9,21] In our study, 7 of 8 patients accepted postoperative radiation, and no locoregional recurrence occurred in 8 cases. For locoregional recurrence, Sun *et al* reported that recurrences may be controlled by salvage surgery with subsequent operation and/or radiotherapy.[20] Until now, there was no evidence for benefits from chemotherapy.[9]

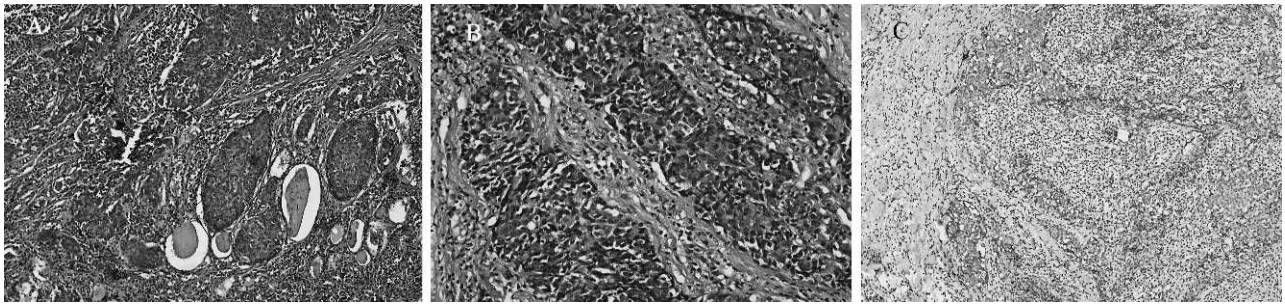

Fig. 4 (A) Solid nests of neoplastic cells are separated by fibrous septa and infiltrated with many lymphocytes; H&E (×100). (B) Tumor cells have indistinct borders and large vesicular nuclei with distinct nucleoli and eosinophilic cytoplasm; H&E (×200). (C) Immunostaining for CD5 shows neoplastic cells with membrane staining; streptavidin perosidase (SP) (×100).

The effect of chemotherapy in CASTLE needs further clinical investigation.

In summary, thyroid CASTLE is a rare malignancy of the thyroid gland. Definite diagnosis requires experienced pathologists and positive CD5 immunoreactivity. Thyroid CASTLE is a low-grade malignant tumor with indolent biologic behavior and favorable prognosis. Radical resection followed by radiotherapy is important to prevent the locoregional recurrence and improve long-term survival.

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