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RESEARCH

Carcinoma Showing Thymus-Like Elements of the Thyroid Gland: Report of Three Cases Including One Case with Breast Cancer History

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Abstract Carcinoma showing thymus-like elements (CASTLE) is a rare malignant tumor of the thyroid or adjacent neck soft tissues, whose histogenesis is still debated. It may resemble other primary or metastatic poorly differentiated tumors histologically and the differential diagnosis is crucial for CASTLE has a better prognosis. However, CASTLE as a second primary tumor has not been reported in the literature. We report three cases of thyroid CASTLE, including a unique tumor following breast-conserving surgery for early-stage breast invasive carcinoma. There were two female and one male. All three tumors were located in the right lobe of the thyroid, and one tumor showed extension into the surrounding soft tissue. Histologically, all tumors showed expansive growth and consisted of cords, nests or sheets of epithelial cells divided into irregularly shaped lobules by fibrous connective tissue with lymphoplasmacytic infiltration. Focal squamous differentiation resembling Hassall's corpuscles were observed. All cases stained positively for CD5, CD117, high molecular weight cytokeratin, cytokeratin, P63, carcinoembryonic antigen and epithelial membrane antigen. Positive staining for Bcl-2 in two cases and chromogranin A in one case was noted. Ki-67 expression ranged from 15 to 25 %. Thyroid transcription factor and CD3 were negative. There was no evidence of recurrent or metastatic disease at following surgery. These features demonstrated CASTLE may arise from branchial pouch remnants, the thyroid solid cell nests. CASTLE is a rare entity, awareness of its occurrence as a second primary tumor is important to avoid overtreatment because it is associated with a favorable prognosis.

Keywords Carcinoma showing thymus-like elements · Breast cancer · Second primary tumor · Solid cell nests · Differential diagnosis · Histogenesis

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Abbreviations

CASTLE	Carcinoma showing thymus-like elements
SCNs	Solid cell nests
H & E	Hematoxylin and eosin-stained
HMWCK	High molecular weight cytokeratin
CK	Cytokeratin
EMA	Epithelial membrane antigen
CEA	Carcinoembryonic antigen
TTF-1	Thyroid transcription factor
CgA	Chromogranin A
CT	Computed tomography

Introduction

Carcinoma showing thymus-like elements (CASTLE) is a rare tumor most commonly occurring in the thyroid and rarely arising in the extrathyroidal soft tissue of the neck. It was first described by Miyauchi et al. as "intrathyroidal epithelial thymoma" in 1985 [1], and was renamed CASTLE by Chan and Rosai in 1991 [2]. It is important to distinguish CASTLE from other poorly differentiated and metastatic tumors as CASTLE is associated with a comparatively favorable prognosis [1, 3].

The histogenesis of CASTLE has long been debated. It has been described to arise from ectopic thymus, vestiges of

thymopharyngeal duct, or branchial pouch remnants [2, 4]. Solid cell nests (SCNs) are usually considered as the remnants of the ultimobranchial body and may represent a pool of stem cells within the adult thyroid [5, 6]. A close histological association between CASTLE and SCNs has been observed [4, 7]. To date there are less than 100 cases of CASTLE have been reported in the English literature [1–4, 7–23], however, CASTLE as a second primary tumor has not been reported. We report three cases of CASTLE, including a unique case occurring in the thyroid after breast-conserving surgery for early-stage breast invasive carcinoma.

Materials and Methods

Case Selection

The surgical pathology files of the Department of Pathology of the First Affiliated Hospital, Medical College of Xian Jiaotong University were searched between January 2005 and November 2012. Three cases of CASTLE were diagnosed according to the WHO classification criteria [24]. The clinical notes and pathologic records including hematoxylin and eosin-stained (H & E) slides were reviewed in all cases.

Immunohistochemistry

Immunohistochemistry was performed on 4 μm, formalin-fixed, paraffin-embedded sections, after baking at 60 °C for 1 h, deparaffinization, rehydration and subsequent incubation with 3 % hydrogen peroxide. Sections were subjected to antigen retrieval in 10 mM citrate buffer (pH 6.0) at 121 °C for 20 min in a steam pressure cooker, followed by a 10 min cool-down step. A panel of primary antibodies (Table 1) was subsequently applied for 30 min at room temperature. Binding of primary antibodies was detected by the EnVision+(rabbit/mouse HRP/DAB+) detection kit (DAKO, Carpinteria, CA). Immunostaining was followed by counter staining with hematoxylin. Positive controls included tonsil (CD5), mast cells (CD117), prostate (high molecular weight cytokeratin, HMWCK), skin (cytokeratin, CK/P63), lymphoid tissue (Bcl-2), cervix (epithelial membrane antigen, EMA), colon (carcinoembryonic antigen, CEA/Ki-67), thyroid (thyroid transcription factor, TTF-1), adrenal medulla (chromogranin A, CgA), and thymus (CD3). Negative controls were performed by substituting the primary antibody with nonimmune mouse immunoglobulins.

Table 1 Panel of antibodies used in the study

Antibody	Type	Clone	Source	Dilution
CD5	M	CD5/54/F6	Dako, Carpinteria, CA	1:30
CD117	P	A4502	Dako	1:500
HMWCK	M	34βE12	Dako	1:25
CK	M	AE1/AE3	Dako	1:50
P63	M	4A4	Dako	1:50
Bcl-2	M	124	Dako	1:100
EMA	M	E29	Dako	1:100
CEA	P	N/A	Dako	1:1000
TTF-1	M	8G7G3/1	Dako	1:200
CgA	M	DAK-A3	Dako	1:500
CD3	M	F7.2.38	Dako	1:100
Ki-67	M	MIB-1	Dako	1:200

M, mouse monoclonal antibody; P, rabbit polyclonal antibody

Immunohistochemical evaluation of sections

Only nuclear staining for P63, TTF-1 and Ki-67, membranous staining for CD5 and CD117, membranous and/or cytoplasmic staining for CD3, and cytoplasmic staining for the other antibodies were considered positive. The sections were evaluated for the percentage of neoplastic cells and the intensity of immunoreactivity. Percentage of cells was recorded as 0 (negative),<5 %, 5–50 %, 51–95 %, and>95 % of cells showing positive staining. Intensity was scored as - (negative), 1+ (weak), 2+ (moderate), and 3+ (strong) [25].

Results

Patient 1

A 37-year-old woman was admitted to the hospital for a routine medical examination. She had undergone breast-conserving surgery for the right breast cancer two years earlier. At the time of surgery, right axillary sentinel lymph node biopsy was negative. Pathologic examination showed a solitary, 1.0 cm × 1.0 cm × 0.8 cm in size, invasive carcinoma of no special type, grade II, without vein tumor thrombus, diagnosed according to the criteria of WHO classification of tumours of the breast (Fig. 1) [26]. Tumor staging was stage pT1bN0M0 according to the American Joint Committee on Cancer modified tumor node metastases (pTNM) classification system [27]. The immunohistochemistry staining of estrogen and progesterone receptors were positive and the score of human epidermal growth factor receptor 2 was 1+ of the breast carcinoma. Due to the 21 gene test had not done and the combined chemotherapy may prevent tumor recurrence, then the patient received adjuvant chemotherapy in the form of epirubicin, cyclophosphamide and docetaxel and a full course of irradiation (50 Gy during a period of 6 weeks using 25 fractions). There was no evidence of a recurrence of breast carcinoma till the last follow-up.

Physical examination revealed a 1 cm, non-tender, hard mass on the right side of the neck, which moved with

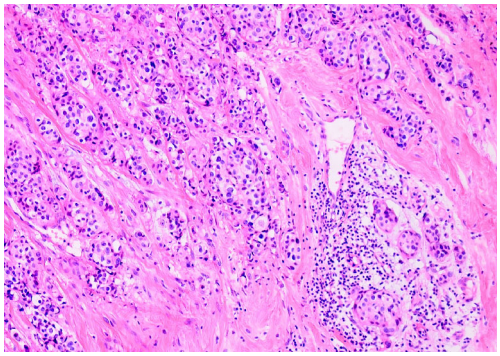

Fig. 1 Cords and trabeculae of breast invasive carcinoma cells with intermediate nuclear grade. The stroma has a less prominent lymphoplasmacytic reaction (H & E 200×, Patient no. 1)

deglutition. Cervical computed tomography (CT) scans demonstrated a mass in the lower portion of the right thyroid lobe measuring 1×1× 0.8 cm. Ultrasonography of the thyroid showed the mass to be homogeneous and hypo-echoic. Serum levels of thyroxine, thyroid-stimulating hormone, and thyroglobulin were within normal limits. The patient underwent a right thyroid lobectomy. There was no evidence of recurrent or metastatic disease at follow-up 6 months after surgery.

Patient 2

A 38-year-old man presented with a history of hoarseness for two months and had no relevant past medical or family history. Physical examination revealed a painless mass measuring approximately 4×3×2.5 cm in the right lobe of the thyroid. The mass was firm to feel and moved with deglutition, with no palpable cervical lymph nodes. Cervical CT scans revealed a homogeneous tumor in the inferior half of the right lobe of the thyroid with tracheal displacement to the left. Routine blood investigations and thyroid function tests were within normal limits. At operation, the tumor measured 3.8×3×2.5 cm and was found to occupy the lower portion of the right lobe of the thyroid. The patient underwent a right thyroid lobectomy with a modified radical neck dissection. There were no signs of recurrent or metastatic disease at 26 months following surgery.

Patient 3

A 29-year-old woman presented with a 7-month history of a mass in the lower half of the neck anteriorly. Physical examination revealed a solitary, non-tender mass in the right lobe of the thyroid, with extensive bilateral cervical lymphadenopathy. The mass measured approximately 6 cm×3 cm×3 cm in size, was firm to feel, slightly mobile and moved with deglutition. Thyroid scintigraphy with 131I showed a cold area in the isthmus and the lower part of the right lobe. Routine blood investigations and thyroid function tests were within normal limits. At operation, a tumor measuring 6×3×3 cm was found to occupy the middle to lower portion of the right thyroid lobe and the isthmus and extended into the surrounding soft tissue. A total thyroidectomy combined with a radical neck dissection was performed. 42 months post-surgery, there were no signs of recurrent or metastatic disease.

Pathological Findings

Macroscopically, all three tumors were lobulated, relatively well-circumscribed, firm and gray-white. The size ranged from 1.0 to 6.0 cm in maximum diameter.

Microscopically, the three tumors showed expansive growth in the thyroid gland without capsular structures, and extended into the surrounding soft tissue in Patient 3. All three tumors consisted of cords, nests and sheets of epithelial cells, divided into irregularly shaped lobules by thick fibrous connective tissue (Fig. 2a and b). Varying amounts of lymphoplasmacytic infiltration were observed among the epithelial cells and in the fibrous stroma (Fig. 3a and b). Nests of tumor cells were penetrated by delicate fine vessels and dilated perivascular spaces with lymphocytic infiltration were found, particularly pronounced in Patient 2 (Fig. 4). Tumor cells were polygonal or spindle-shaped with a round to oval, vesicular nucleus with 1 or 2 small nucleoli. The cytoplasm

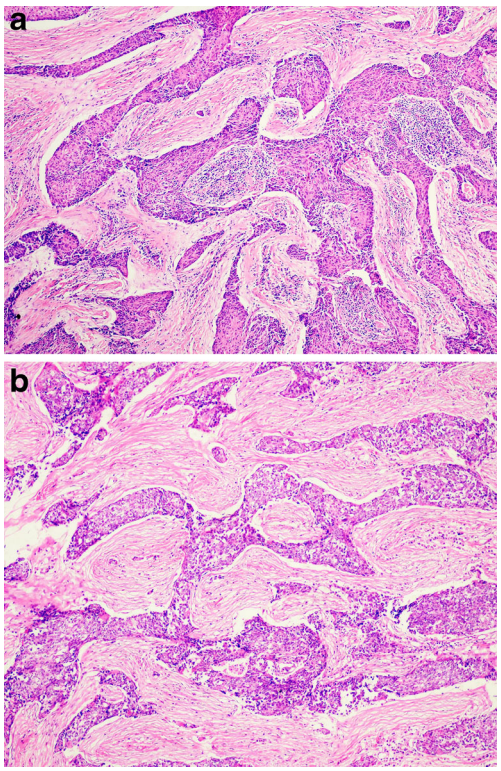

Fig. 2 Cords, nests and sheets of epithelial neoplastic cells were divided into irregularly shaped lobules by thick fibrous connective tissue (H & E 40×, **a**, Patient no. 1; **b**, Patient no. 3)

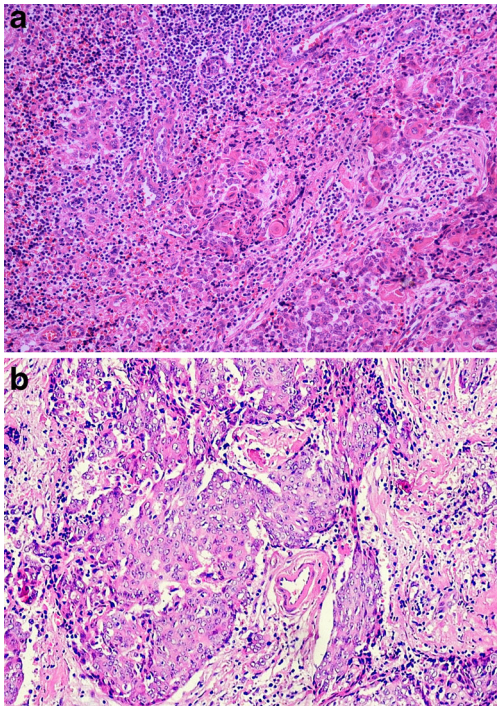

Fig. 3 Varying amounts of lymphoplasmacytic infiltration (H & E 100×, **a**, Patient no. 1; **b**, Patient no. 2)

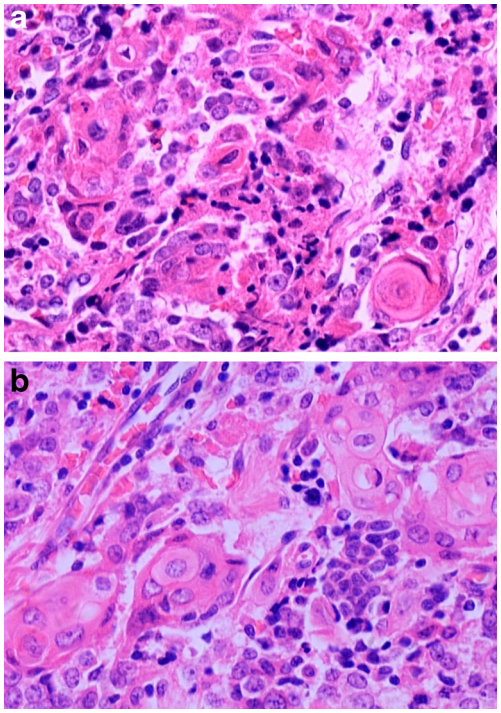

Fig. 5 Focal definite squamous differentiation with formation of intercellular bridges and keratinization in concentric whorls resembling Hassall's corpuscles (H & E 400×, a, Patient no. 1; b, Patient no. 3)

was slightly eosinophilic to amphophilic and showed indistinct cell borders. Focal definite squamous differentiation with formation of intercellular bridges, and keratinization in concentric whorls resembling Hassall's corpuscles were observed in all patients (Fig. 5a and b). There was no coexisting papillary or follicular carcinoma. Mitotic figures averaged 1 to 2 per 10 high power fields. There was no evidence of marked nuclear pleomorphism, necrosis or lymph node metastases in any of the patients.

The immunohistochemical results are summarized in Table 2. The majority of the neoplastic cells of all cases were positive for CD5 (Fig. 6a), HMWCK, CK, P63 and CD117 (Fig. 6b) with moderate to strong diffuse staining. Staining for Bcl-2 was positive in 2 cases and for CEA was positive in all 3 cases, with weak to moderate staining. EMA (Fig. 6c) was positive with moderate staining in the regions with squamous differentiation. CgA was focally positive in 1 of 3 cases with weak staining. The neoplastic cells were negative for TTF-1 and CD3. The proliferation marker Ki-67 expression ranged from 15 to 25 % with moderate staining. The majority of lymphocytes infiltrating the neoplastic nests were T cells, staining positively for CD3 and CD5.

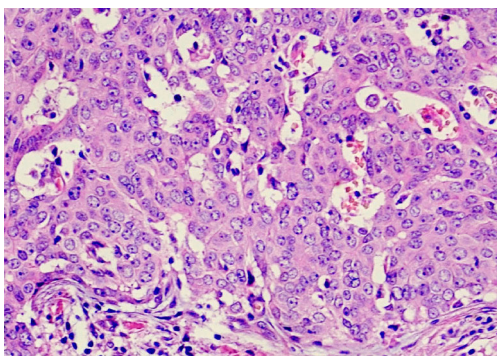

Fig. 4 Nests of neoplastic cells were penetrated by fine vessels, and dilated perivascular spaces with lymphocytic infiltration (H & E 200×, Patient no. 2)

Table 2 Immunohistochemistry findings

Antibody	Case 1		Case 2		Case 3	
	Positive cells (%)	Intensity	Positive cells (%)	Intensity	Positive cells (%)	Intensity
CD5	90	3+	80	2+	80	2+
CD117	90	3+	90	3+	90	2+
HMWCK	95	3+	95	3+	95	3+
CK	95	3+	95	3+	95	3+
P63	95	3+	90	2+	95	3+
Bcl-2	20	1+	0	–	30	2+
EMA	5	2+	5	2+	<5	2+
CEA	20	1+	15	2+	30	2+
TTF-1	0	–	0	–	0	–
CgA	0	–	<5	1+	0	–
CD3	0	–	0	–	0	–
Ki-67	25	2+	15	2+	20	2+

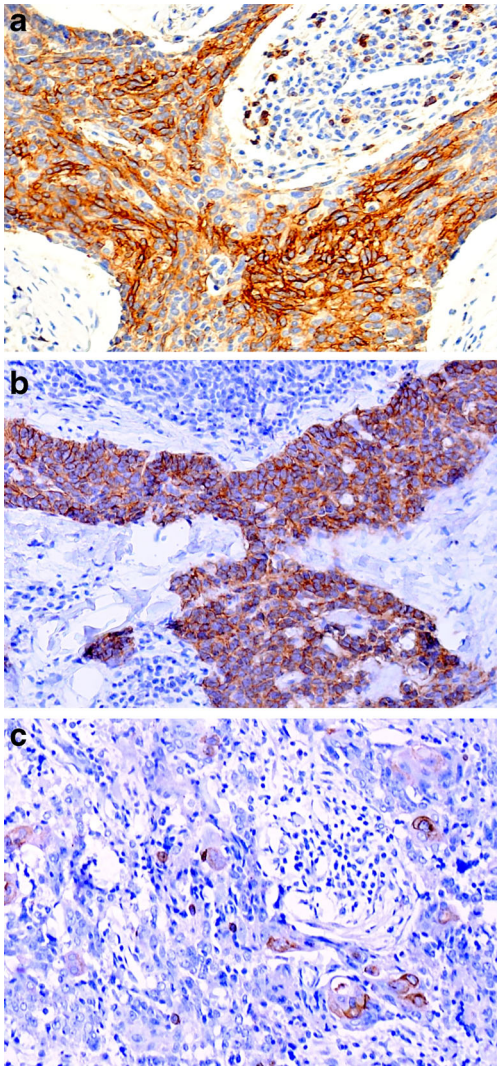

Fig. 6 Immunohistochemical findings (200×) (**a**) Strong and diffuse positive for CD5 of the neoplastic cells and T lymphocytes (Patient no. 1); (**b**) Strong and diffuse positive for CD117 of the neoplastic cells (Patient no. 2); (**c**) Moderate positive for EMA of the neoplastic cells in the regions showing squamous differentiation (Patient no. 3)

Discussion

CASTLE is a rare cervical tumor [3, 7, 24] which has not been reported with a history of previous or subsequent tumor to the best of our knowledge. It is important to be aware of this diagnosis, because histologically CASTLE resembles other poorly differentiated tumors such as primary or metastatic squamous cell carcinoma of the thyroid, undifferentiated carcinoma with squamoid features, but its clinical course is protracted and seems comparatively favorable [3, 14, 24]. Among the three CASTLE reported, the tumor of Patient 1 was resected in view of the clinical suspicion of thyroid metastasis of breast carcinoma and finally was confirmed by its morphological characteristics. We highlighted that CASTLE may occur as a second primary tumor thus it is crucial to make the accurate diagnosis to avoid overtreatment.

Histologically, prominent features of CASTLE include: (a) lobulation on cut surfaces; (b) expansive growth pattern; (c) thick fibrous bands dividing the tumor; (d) the presence of abundant lymphocytes; (e) perivascular spaces with lymphocytes; (f) Hassall's corpuscle-like structures; (g) oval, vesicular nuclei, sharply defined nucleoli, and pale cytoplasm; (h) rare or infrequent mitoses; (i) absent or limited coagulative necrosis; and (j) lack of foci of anaplastic, papillary, or follicular tumor [1, 11]. In the patients we have reported, all of the characteristics were identified, especially keratinization and true intercellular bridges. In contrast, breast invasive carcinoma of no special type lacks these histological features. As in our Patient 1, the breast carcinoma cells were arranged in cords and trabeculae, with intermediate nuclear grade. The cytoplasm were slightly eosinophilic. Mitotic figures averaged 8 per 10 high power fields. The stroma has a less prominent lymphoplasmacytic reaction.

Using a panel of immunohistochemical antibodies was helpful in differential diagnosis. Like thymic carcinomas, most cases of CASTLE are positive for CD5 and CD117 and negative for the usual thyroid markers [28, 29]. CD5 is negative in squamous cell carcinoma, poorly differentiated carcinoma, follicular adenoma/carcinoma, most of papillary carcinoma of the thyroid, other head and neck tumors [16, 29], and breast carcinomas [30]. Ito et al. reported that the sensitivity and specificity of CD5 for the diagnosis of CASTLE was 82 and 100 % respectively [3]. Reimann et al. demonstrated that the expression of CD5, HMWCK, CEA and p63 in CASTLE were useful markers to confirm the diagnosis [4]. The immunohistochemical results in our reported cases were consistent with the reported profiles. The histological features and immunohistochemical staining results supported the diagnosis of CASTLE as a primary tumor, rather than breast cancer metastasis to the thyroid gland in Patient 1. Additionally, a few cases with features of neuroendocrine differentiation have been reported, as one of our cases showing focal positivity for CgA [12, 14].

Several studies have revealed that women with a history of breast cancer have a higher risk for a second primary cancer than the general population [31–33]. Specifically, breast and thyroid cancer have been observed to occur more frequently than expected as multiple primary tumors in women [34]. Mamounas et al. reported 15 cases of second primary thyroid cancers in breast cancer patients with most being papillary carcinomas (47 %), followed by follicular carcinomas (20 %) and mixed carcinomas (13 %) [35]. The excess risk for a second primary thyroid cancer may be due to shared risk factors, such as genetic, hormonal or environmental factors, or a result of the adjuvant therapy of breast cancer, such as radiotherapy, chemotherapy and hormonal therapy [31, 36]. Although there was lack of direct evidence showing the occur

of the two kinds of tumor have some potential relationship and it may be an accident, we speculated that these risk factors may have promoted the development of CASTLE after breast cancer in Patient 1.

The histogenesis of CASTLE has been long debated [2, 7]. On the basis of the histological and immunohistochemical features, it has been postulated that CASTLE may arise from ectopic thymus, vestiges of thymopharyngeal duct, or branchial pouch remnants present in the soft tissue of the neck or within the thyroid gland [2]. SCNs are thought to be derived from ultimobranchial body remnants, which derive from the fourth and fifth branchial pouch and are composed of epithelial cells [4]. Although the biological significance of SCNs remains unclear, a potential stem cell role for SCNs in the thyroid along with a histogenetic link between SCNs and papillary or mucoepidermoid thyroid carcinomas has been postulated [5, 6, 37–39]. A comparative study by Reimann et al. showed that CASTLE and SCNs have a similar immunohistochemical profile, suggesting that CASTLE is probably of thymic origin and may arise from SCNs [4]. Veits et al. demonstrated that CASTLE was characterized by chromosomal imbalances similar to those found in thymomas and thymic carcinomas indicated a similar sequence in tumor development [19]. Recently, Pusztaszeri et al. reported a unique CASTLE arising in close association with SCNs, the merging of CASTLE and SCNs cells raised the possibility that SCNs may have been the precursor lesion [7]. In our three cases, the results of immunohistochemical staining supported CASTLE may arise from SCNs, although a direct continuity between SCNs and CASTLE was not observed.

In conclusion, to the best of our knowledge, this is the first study of CASTLE of the thyroid as a second primary tumor following breast cancer. Our study supports the suggestion that CASTLE arises from SCNs also. It highlights the importance of CASTLE as a possible diagnosis when investigating a neck lump suspicious for metastatic disease, while it might be interesting to investigate a potential relationship between the metachronous appearance of CASTLE and breast cancer.

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