

Two Contrasting Cases of Carcinoma Showing Thymus-Like Differentiation (Castle) of the Thyroid

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ABSTRACT

Carcinoma showing thymus-like differentiation (CASTLE) is a rare malignant tumor originates from remnant thymus tissue of thyroid. We encountered two cases of CASTLE and each case illustrated the varied clinical manifestations. Case 1 was a 46-year-old female patient that had already been diagnosed with papillary thyroid carcinoma by Fine Needle Aspiration Cytology (FNAC). The main complaint was a gradually growing, painless anterior neck mass that appeared two years ago. Total thyroidectomy was performed and the final diagnosis was CASTLE. Case 2 was a 70-year-old male patient seeking a correct diagnosis for a thyroid mass. He complained of hoarseness and obtuse neck pain that persisted for one year. Since CASTLE was highly suspected by FNAC, we performed total thyroidectomy with lymph node dissection. In contrast to Case 1, the operation was extremely difficult, as the tumor appeared to have permeated the adjacent musculature. We herein discuss clinical features of CASTLE cases, particularly with regard to the preoperative imaging diagnosis, FNAC, and surgical procedure.

INTRODUCTION

Carcinoma showing thymus-like differentiation (CASTLE) is a rare malignant tumor that originates from the thyroid or adjacent remnant thymus tissue and was first described by Miyauchi et al. as intrathyroidal epithelial thymoma [1-3]. Specific diagnostic methods and optimal therapeutic modalities of this tumor have yet to be established [4]. For example, diagnosing CASTLE by using preoperative Fine Needle Aspiration Cytology (FNAC) is extremely difficult [5-10]. In cases of CASTLE, the most frequent preoperative FNAC diagnosis is malignant tumor of unspecified classification [6,7,10]. In contrast, CASTLE has been shown to exhibit determinative histopathological features [1,2,8,9]. Another definitive marker for CASTLE is the immunohistochemical detection of the CD5 thymic marker on tumor cells [3-9,11]. While Computed Tomography (CT) scan and ultrasonography (US) are the most frequent methods used in preoperative examination for various thyroid tumors, CASTLE lacks definitive findings except for the absence of calcification in the tumor [12-14]. In general, CASTLE patients have a good prognosis provided the tumor is completely resected with or without lymph nodes dissection [4]. In addition, post-operative radiation therapy and/or chemotherapy [15-19] are significant supportive therapeutic modalities for CASTLE that can improve prognosis. In contrast, lymph node metastasis in patients affected with CASTLE did not promote recurrent disease [4]. However, radical surgery with neck dissection is commonly performed in CASTLE cases due to the difficulty of

determining exact preoperative diagnoses [19]. This study presents two cases of CASTLE that showed contrasting clinical manifestations, particularly with regard to the imaging diagnosis, FNAC and surgical procedure.

CASE PRESENTATION

Case 1: A 46-year-old Japanese female patient was referred to our institution for surgical treatment of a thyroid malignancy that had already been diagnosed as Papillary Thyroid Carcinoma (PTC) by FNAC. Her main complaint at the time of presentation was a gradually growing, painless anterior neck mass on the right side that had appeared two years ago. The mass was well-demarcated and exhibited good mobility on palpation. Pre-contrast CT scan showed solid, uniform and well-delineated tumor in the right-lower lobe without calcification. The attenuation of the tumor was lower than that of normal thyroid tissue. Contrast-enhanced CT scan represented slightly enhanced tumor with a normal plane between the tumor and the thyroid although the tumor showed partially indistinct border adjacent to the musculature (Figure 1A and B). Magnetic Resonance Imaging (MRI) of the tumor represented homogeneously isointense on T1-weighted imaging and mildly hyperintense on fat-suppressed T2-weighted imaging with well-circumscribed border (Figure 1C). After reviewing the FNAC specimen (Figure 2A and B) that had been examined by her previous physician and pathologist, we decided that the most suitable course of action was surgical intervention.

Total thyroidectomy accompanied with neck dissection of level II to VI and the upper mediastinal lymph nodes was subsequently performed. Neck dissection was performed concurrently in consideration of the initial preoperative diagnosis of PTC with suspicion of capsular invasion, and there was a possibility of existing microscopic lymph node metastases. We then completely removed the tumor along with the adjacent muscular tissue that was judged intraoperatively to provide sufficient surgical margins. The resected tissue consisted of an elastic hard tumor covered by thin connective tissue, measuring 3.8x3x2.2 cm with a whitish-gray and solid cut surface (Figure 3 A and B). Unexpectedly, our final histopathological diagnosis turned out to be CASTLE of the thyroid gland. The tumor was lobulated by fine connective tissue (Figure 4A), which consisted of eosinophilic cells with polygonal nuclei. A Hassall's body-like structure was also

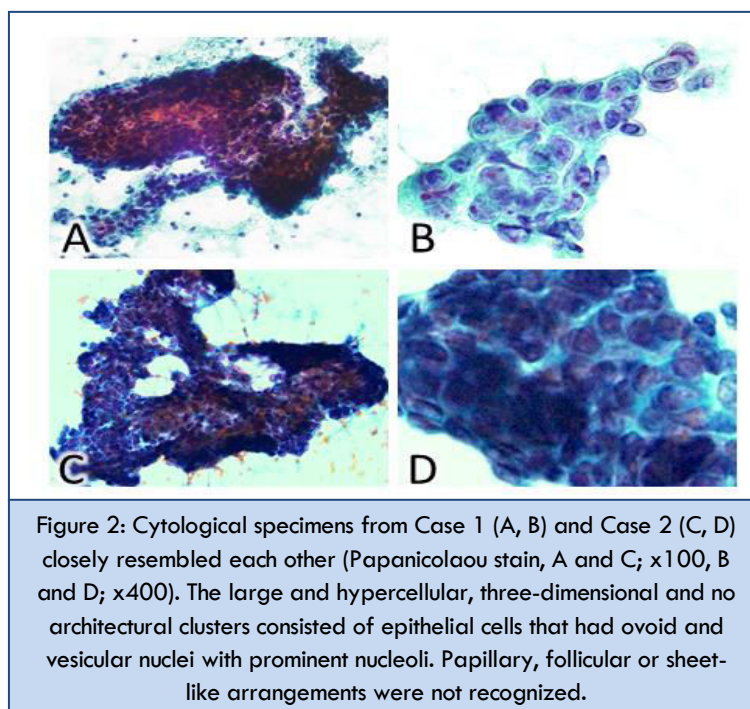
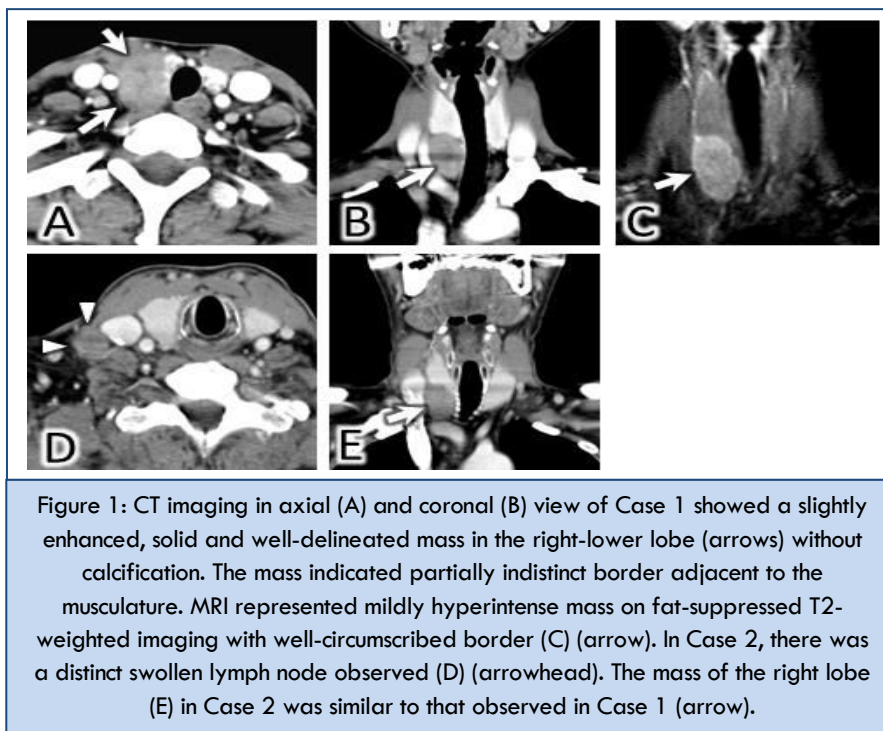
evident (Figure 4B). Immunohistochemistry showed that CD5 was strongly positive (Figure 4C). Thyroid Transcription Factor 1 (TTF-1), thyroglobulin and calcitonin were negative. We carefully reevaluated the preoperative FNAC specimen of Case 1 with pathologists who had diagnosed the surgically resected specimen of this case. As a result, we made a decision that her FNAC specimen would be highly suspicious of CASTLE because these cell clusters lack typical cytological features of PTC (Figure 2). Since lymph node metastasis and vascular invasion were not detected, adjuvant therapy was not performed. Recurrent or metastatic disease has not occurred during the four-year follow-up.

Case 2: A 70-year-old Japanese male patient visited our department while seeking to obtain a correct diagnosis for a thyroid mass. He complained of hoarseness and obtuse neck pain that was present over the past one year. CT scan showed that there was a weakly-enhanced and well-demarcated tumor located at the lower part of his right thyroid lobe. Other than our uncertainty regarding lymph node metastasis, his findings were quite similar to Case 1 (Figure 1D and E). After performing FNAC, CASTLE of the thyroid was highly suspected (Figure 2C and D). Total thyroidectomy with dissection of the regional lymph nodes was planned. Preoperative MRI could not be performed because his dental implant could not tolerate strong magnetism.

During the operation, the operative procedure proved to be extremely difficult, as compared to Case 1. In this case, the connective tissue that surrounded the tumor was very thick, and appeared to deeply permeate the adjacent musculature. Therefore, after we removed the adhered tumor from the border of the normal tissue, cryosections of surgical margins were prepared for intraoperative consultation to establish a diagnosis. Figure 3C and D show the surgically resected thyroid tumor. The markedly lobulated tumor was covered by thick fibrous tissue in this section, which measured 3.5x3x2.5 cm. The final histological diagnosis was CASTLE (Figure 4D and E) with massive lymphocytic aggregation in the peripheral stroma. Immunohistochemical evaluation showed similar positive CD5 results as Case 1 (Figure 4F). TTF-1, thyroglobulin and calcitonin were negative. The surgical margins were negative for tumor cells in the permanent sections, with a large metastatic focus detected from level II to VI in one of the ten

dissected lymph nodes. Based on this histopathological result, external beam radiation of 50Gy in 25 fractions was promptly performed to inactivate any residual tumor cells left. Local

recurrence or distant metastases has been absent during the two-year postoperative period.



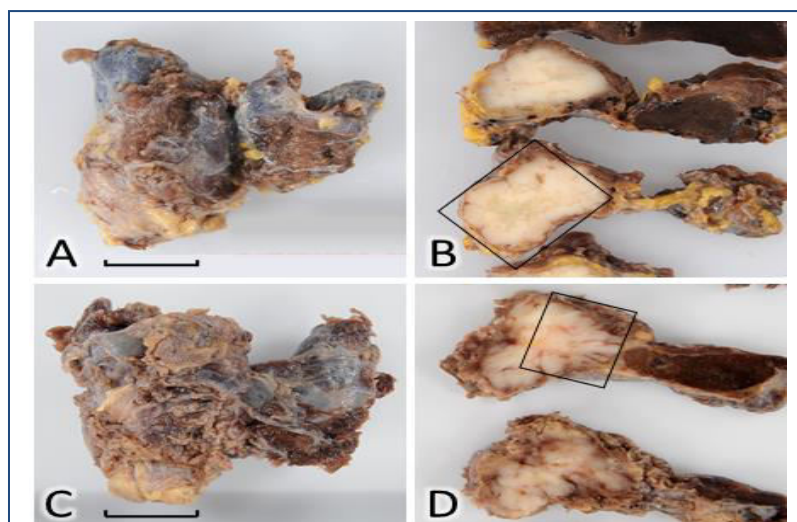


Figure 3: Surgically resected thyroid from Case 1 (A) showed an elastic-hard tumor that measured 3.8x3x2.2 cm with a whitish-gray and solid cut surface bordered by thin connective tissue (B). In Case 2, the resected thyroid with adjacent fibro-muscular tissue (C) exhibited a lobulated tumor with thick fibrous tissue in the cut section that measured 3.5x3x2.5 cm (D). Bar; 2cm. The quadrangles are equivalent to the low-power views of Figure 4A and 4D.

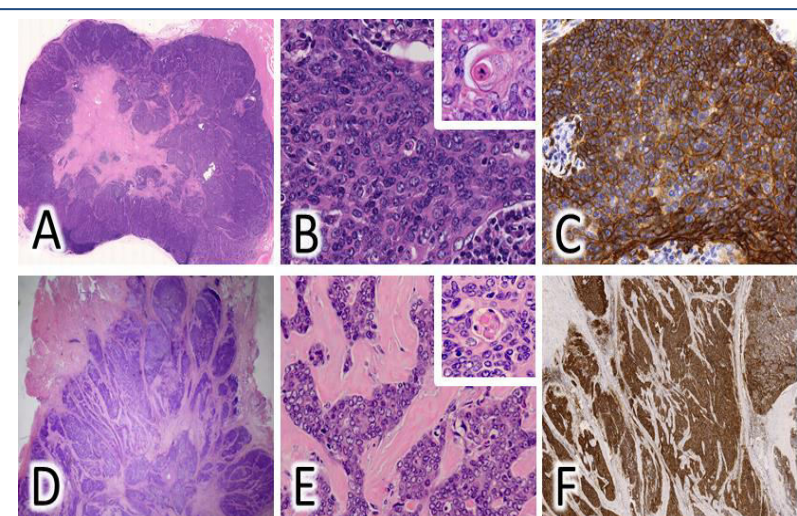


Figure 4: Resected tissue from Case 1 exhibited a solid and uniform tumor bordered by fine connective tissue, and clearly separated from the adjacent tissue (A) (HE, x6). Eosinophilic tumor cells exhibited vesicular nuclei with scanty eosinophilic cytoplasm (B) (HE, x200). There was also a small number of Hassall's body-like structures (inlet) recognized. CD5 was strongly positive accordant with tumor cells (C) (x100).

In Case 2, the tumor was accompanied by massive and dense fibrous components (D) (HE, x8). The cytological features resembled those seen in Case 1 with the exception of the existence of thick hyalinized stroma (E) (HE, x200). A vague Hassall's body-like structure (inlet) was also observed. Tumor cells featured marked CD5 reactivity that was similar to as Case 1 (F, x20).

DISCUSSION

We evaluated two contrasting cases of CASTLE, with Case 1 diagnosed postoperatively and Case 2 diagnosed preoperatively. Case 1 was a female in her 40s with a painless neck mass, while Case 2 was a 70-year old male with complaints of obtuse pain and lymph node metastasis. Although the clinical manifestations of CASTLE were similarly varied, our present study further evaluated the preoperative diagnosis, pathological features and surgical treatment of this rare tumor. The determinative preoperative diagnostic evidence for this tumor has yet to be well established particularly in FNAC diagnosis [5-10]. In fact, Chang et al. [10] reviewed preoperative FNAC that had been performed in 40 cases of CASTLE, and reported that the most frequent cytological diagnoses in these cases was malignant tumor not otherwise specified. In contrast, there is literature attempting to address the diagnostic challenge of FNAC. Cappelli et al. [5] reported an aggressive case of CASTLE with pleural dissemination, with the conclusion that CD5 positivity on malignant cells were grounds for CASTLE diagnosis while these malignant cells were not otherwise specified. In addition, Hirokawa et al. summarized the following cytodiagnostic characteristics of CASTLE [6,9]; Solid cell clusters are large and hypercellular, three-dimensional and have no internal structures i.e. papillary, follicular, sheet-like or colloid arrangements. The tumor cells may show squamous differentiation. They also emphasized that poorly differentiated cells with individual cell keratinization or squamoid structures found during the FNAC should be taken into consideration when CASTLE was suspected in a patient. In the current cases, the thyroid tumor of Case 1 was initially diagnosed as PTC by the patient's previous pathologist, while Case 2 was preoperatively judged as CASTLE by a pathologist in our institution. Cytological finding of Case 1 was quite similar to Case 2, and these cytological pictures are compatible with CASTLE, therefore Case 1 could have been misinterpreted cytologically due to the disease rarity.

The histological diagnosis of CASTLE in surgically resected specimens is not considered difficult when the evaluations are based on the following morphological features: lobulation on cut surfaces separated by fibrous stroma with lymphocytic aggregation; solid or follicular proliferation of eosinophilic epithelial cells with fairly abundant cytoplasm; rare or

infrequent mitoses; lack of foci of anaplastic, papillary, or follicular tumor; large vesicular nuclei and prominent nucleoli [1,2,8]. In addition, the appearance of a Hassall's body-like pattern or focal squamoid differentiation [1,9] is suggestive of a thymic origin. Moreover, strong immunoreactivity for CD5 provides valuable evidence of a thymus-like differentiation [3,9-11]. Differential diagnosis of CASTLE includes benign thymoma and undifferentiated carcinoma, squamous cell carcinoma, follicular carcinoma and solid variant of papillary carcinoma with squamous differentiation of the thyroid, and metastatic squamous cell carcinoma particularly from the upper aerodigestive tract and lung [2,8].

CASTLE lacks definitive findings particularly when CT, US and MRI are performed preoperatively. In fact, Wu et al. [13] reported CT and MRI features of ten CASTLE cases and they concluded that CASTLE has no characteristic imaging compared with other thyroid tumors. However, several reports indicated absence of calcification in the tumor by CT or US may help to differentiate diagnosis with PTC [12,14]. Ahuja et al. [14] used precise MRI studies to evaluate potential CASTLE case, and concluded that the method was able to show the particular lobulated outline of the tumor. Moreover, the authors reported that since the lobes of the tumors found in CASTLE cases are separated by fibrous tissue, the possibility exists that the cut surfaces of these specimens might be visible in MRI. In our cases, MRI of Case 1 was not otherwise specific, but if MRI had been performed in Case 2, the lobulated pattern suggested by Ahuja et al. might have been detected preoperatively. CASTLE tumors most frequently occur in the lower portion of the thyroid, as the tumor is thought to arise from a thymus remnant that failed to descend during embryonic development [1,4,12]. Therefore, if a thyroid mass is shown to be located within the lower portion of the thyroid, helpful findings may be provided by CT and MRI such as our cases.

Recently Ge et al. [4] reviewed 82 cases of CASTLE, and found that 81 of the patients had undergone surgery. When the authors evaluated the effects of lymph node metastasis and radiotherapy on recurrence, they found that lymph node metastasis did not promote recurrent disease following radical surgery, and that postoperative radiation did not reduce recurrence rate. Despite these reported findings, radical

surgery with neck dissection is still commonly performed because in most cases, preoperative examinations are unable to specifically diagnose CASTLE. In fact, about 68% of all CASTLE cases that have been reported underwent thyroidectomy with lymph node dissection as primary surgery [19]. On the other hand, radiotherapy and chemotherapy are thought to be supportive therapeutic modalities for CASTLE including recurrent cases. Although the curative efficacy appears variable, we recommend that post-operative radiation therapy should be considered for patients with positive nodal status [15-19].

Details on the intraoperative situations associated with CASTLE have rarely been reported. In our current patients, we decided that the tumor in Case 1 could be removed since the surgical margins at the time of the operation were large enough and because the tumor exhibited small amounts of thin fibrous tissue at the point where it adhered to the margins. In contrast, the tumor in Case 2 had extremely thick connective tissue that surrounded the tumor, and which appeared to deeply permeate the adjacent musculature on gross inspection. However, the intraoperative frozen section diagnosis showed that the tumor cells did not permeate the adjacent tissue. Kakudo et al. [15] described that CASTLE is usually a well-circumscribed tumor with a sharp border, but is not encapsulated with fibrous capsule. The reason for the thick surrounding connective tissue in Case 2 is still unknown. Therefore, even when there is thick fibrosis with marked lymphocytic aggregation suggestive of adjacent tissue invasion, a complete resection should be attempted in suspected CASTLE cases.

The reason is still unclear why majority of CASTLE patients in the literature were from Asia such as our cases. Only 19 cases of maldescended thymic tissue near the thyroid gland were reported among 3,236 pediatric autopsied cases [20]. The rarity of CASTLE is accurately reflected in these data because CASTLE originates from thymus remnant near the thyroid. Future analysis of genetic factors among races may be useful to clarify this rare tumor's onset.

CONCLUSIONS

CASTLE is a rare malignant tumor and a tumor in which preoperative cytological diagnosis is very difficult. Otolaryngologists need to consider the possibility of this tumor

even when other ordinary malignancies, such as PTC, have already been diagnosed.

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