Clinical Utility of Fine Needle Aspiration Cytology for Adenoid Cystic Carcinoma of the Trachea with Thyroid Invasion: A Case Report

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**Background:** Adenoid cystic carcinoma of the trachea (ACCT) is a rare cancer; ACCT with thyroid invasion is particularly rare. We first suspected anaplastic thyroid carcinoma (ATC) but diagnosed ACC after performing fine needle aspiration cytology (FNAC). A tracheal origin was confirmed after operation.

**Case Description:** We report the case of a 77-year-old female presenting to our hospital with acute inspiratory dyspnea requiring emergency tracheotomy. Physical examination revealed a right anterior neck swelling with a hard and unmovable mass. Computed tomography (CT) and ultrasonography (US) showed tumor extension to the right thyroid lobe, and between the first and third tracheal rings, which caused severe stenosis of the lumen. Next, we performed FNAC. Clinical findings were highly suspicious for ACCT with thyroid invasion. Thirty-five days after the first visit to our department, the patient underwent total laryngectomy, cervical esophagectomy, and thyroidectomy with bilateral selective neck dissections at another hospital. The tumor was located in the right posterior wall of the trachea, with extension into the right thyroid gland. Pathological examination showed an infiltrative carcinomatous proliferation with tubular and cribriform patterns. The tumor was classified as pT4N1. A definite diagnosis was made after histopathological analysis of the surgical specimen confirmed ACCT. The tumor was found to be positive for FABP7, a putative prognostic marker of ACC, and metastasized to the lungs 3 years
after the surgery.

**Conclusions:** ACCT with thyroid invasion is an extremely rare malignant neoplasm. FNAC was useful for differentiating ACCT from other diagnoses and enabled appropriate surgical treatment.

Key words: Fine Needle Aspiration Cytology (FNAC), Adenoid Cystic Carcinoma (ACC), Adenoid Cystic Carcinoma of the Trachea (ACCT), Anaplastic Thyroid Carcinoma (ATC), fatty acid binding protein 7 (FABP7)

**Running title:** Clinical Utility of FNAC for ACCT with Thyroid Invasion
Introduction

Adenoid cystic carcinoma (ACC) is a rare cancer with an annual incidence of less than 6 per 100,000 population\(^1\). ACC was first described as cylindroma by Billroth in 1853, with its current name proposed by Spies in 1930\(^2\). ACC is categorized into three subtypes. It typically presents with a cribriform pattern. A tubular form shows good prognosis, whereas the third subtype is solid and is characterized by poor outcomes. ACC of the trachea (ACCT) is rare, with an overall annual incidence of less than 0.2 per million\(^3\). ACCT with thyroid invasion is extremely rare. The predominant clinical symptoms of ACCT are dyspnea and hoarseness, and the tumor is slow-growing malignancy.

Anaplastic thyroid carcinoma (ATC) is the most aggressive type of thyroid cancer, and indeed one of the fastest-growing and most aggressive of all cancers. ATC is rare, being found in less than 2% of patients with thyroid carcinomas. Some patients with ATC present with acute respiratory symptoms because of the tracheal invasion.

Fine needle aspiration cytology (FNAC) is an important diagnostic tool because of its simplicity, safety, and cost-effectiveness. It is becoming a popular procedure for diagnosing thyroid diseases.

In this case, we initially suspected ATC. The original site of the tumor could not be identified through paraclinical investigation. Emergency tracheotomy was required
because of acute inspiratory dyspnea. After this procedure, we conducted FNAC and diagnosed ACC. The tracheal origin of the tumor was confirmed only after pathological examination and diagnosis of the operative specimen. In the present paper, we described the case of tracheal adenoid cystic carcinoma extending into the thyroid gland, which apparently looked like thyroid carcinoma in the radiological examination but was successfully diagnosed by FNAC.
Case report

A 77-year-old Japanese woman with a history of duodenal ulcer, ganglion cyst of the knee, and iodinated contrast dye allergy presented to the thyroid hospital with acute inspiratory dyspnea that required emergency tracheotomy. She had suffered from hoarseness for 4 months.

Physical examination revealed right anterior neck swelling with a hard and unmovable mass. Laboratory tests showed that blood levels of thyroid function (fT4: 1.3 [ng/dl], fT3: 2.9 [pg/ml], TSH: 1.45 [µIU/ml]), CEA [3.6 ng/ml] and calcitonin [1.8 pg/ml] were within the normal range. Computed tomography (CT) and ultrasonography (US) revealed a tumor extending to the right thyroid lobe and peritracheal tissue, as well as severe stenosis of the lumen between the first and third tracheal rings (Fig. 1). Imaging showed extension of the tumor obstructing the trachea, but we could not determine the original tumor site and it was difficult to distinguish the cervical esophagus from the mass.

We then performed FNAC of the upper right lobe of the thyroid with a 22-gauge needle under US guidance. The specimens were stained using the Papanicolaou method. At medium power, aspiration cytology revealed loosely cohesive sheets and three-dimensional clusters of tumor cells against a clear background (Fig. 2A). Under high power, aggregates of small round cells surrounding light green homogeneous material
were observed (Fig. 2B). These cells had limited cytoplasm, indistinct cytoplasmic borders, and evenly distributed chromatin. Pale green globules near the tumor cells were noted (Fig. 2C). These cytological features are suggestive of ACC. No other characteristics indicative of ATC or other thyroid carcinomas were observed. The medullary carcinoma was also ruled out by the blood data. On the basis of the clinical data, invasion of tracheal ACC into the thyroid gland was strongly suspected rather than tracheal invasion by thyroid carcinoma.

Since the lesion had spread to the trachea, thyroid gland, and cervical esophagus, it was thought to require pharyngo-laryngo-esophagectomy, and the patient was referred to a hospital specializing in head and neck cancer. The patient was transferred and underwent total pharyngo-laryngo-esophagectomy, and thyroidectomy with bilateral selective neck dissection (level II–IV). Macroscopic observations confirmed the tracheal location of the tumor (Fig. 3). The tumor was located in the right posterior wall of the trachea, between the cricoid cartilage and the third tracheal ring with extension to the right thyroid gland. The tumor was 5.3 × 3.2 × 2.8 cm in size. Pathological examination showed that the tumor originating from the trachea had directly infiltrated the adjacent thyroid gland (Fig. 4A), and that the surrounding soft tissue in contact with the wall of the esophagus was involved (Fig. 4B). The tumor cells were arranged in tubular and
cribriform patterns that suggested ACC. Immunohistochemical expression of fatty acid binding protein 7 (FABP7) was apparent (Fig. 4C). Overall, the tumor exhibited morphological features consistent with ACCT. It has been suggested that FABP7, a Notch signaling-related protein, could be a prognostic marker for ACCT. TNM staging was performed using the system proposed by Bhattacharyya for staging primary ACCs of the trachea. The tumor was classified as pT4N1 (T4: spread to adjacent organs or structures, N1: clinical or histological evidence of regional nodal disease) because it had infiltrated the thyroid gland and adjacent soft tissue, and invaded the perineural and muscle tissues. There were metastases to bilateral regional neck lymph nodes. Histopathology provided a definitive diagnosis of ACCT. Three years after surgery, lung metastases were observed.
Discussion

We herein report the case of a 77-year-old female who was suspected to have a rare thyroid-invading ACTT that apparently looks like anaplastic thyroid carcinoma on FNAC. Only 10 cases of primary ACC with thyroid invasion have been reported to date\(^5\). Approximately one-third of patients with ACC develops distant metastasis to common sites such as the lungs, brain, bone, and liver. Of these 10 cases, 6 had primary tumors originating in the trachea. The others include 3 cases of laryngeal minor salivatory gland and 1 case of left parotid. These six patients included two males and four females, with an average age of 49 years (ranging from 17 to 68). Elder patient of ACCT in this case was rare. Their clinical presentations consisted primarily of respiratory symptoms, such as asthma, cough, dyspnea, hoarseness, hemoptysis, wheezing, and neck pain. Three of the six patients showed multiple organ involvement, rather than only the trachea, and five underwent surgical treatment. FNAC was performed preoperatively for four of the 10 cases, and they were diagnosed as ACC\(^6,7,8,9\). Radiotherapy was administered in five cases and chemotherapy in the remaining case. In this case, because of the patient's advanced age, no additional locoregional treatment such as irradiation was performed.
In the present case, a CT scan showed the thyroid and tracheal masses, but failed to reveal the relationship between them. In fact, we initially suspected ATC. A previous report showed that ACCT extending into the thyroid gland mimics thyroid carcinoma in CT imaging$. FNAC$ is useful in differentiating the two because the diagnosis of ACC and ATC by FNAC is usually easy. However, it should be noted that in the case of ATC, the quality of the samples is sometimes inadequate for FNAC sampling. The main reasons for it are below; 1) tumor regressive changes (necrosis, hemorrhage, leukocytic infiltration), 2) extensive tumor fibrosis, and 3) distinct differentiated and anaplastic patterns in the same tumor$. In addition, immunohistochemistry may also be necessary for accurate cytopathological and histopathological diagnosis$. We performed FNAC on the upper right lobe of the thyroid, after which we strongly suspected invasion of tracheal ACC into the thyroid gland. Therefore, we suggest that a CT scan and FNAC should be completed preoperatively in cases of this type to facilitate earlier diagnosis.

ACCT is very rare, but new genetic findings have been reported in recent literature. Little is known about the expression and clinical significance of Notch1 and its target gene, FABP7, in tracheal and bronchial ACC. The Notch pathway is involved in stem cell maintenance, cell proliferation, and angiogenesis$. Ferrarotto at al. found that the
majority of Notch1 mutations in ACC were activating. Strong expression of FABP7 was observed in glioblastoma, breast cancer, and renal cancer, and was significantly associated with poor survival. Xie M\textsuperscript{15} reported that Notch1 and FABP7 were overexpressed in 37.8\% and 38.3\% of 368 patients with tracheobronchial ACC, respectively. Moreover, overexpression of Notch1 and FABP7 were independent prognostic indicators for recurrence-free survival (RFS) in a multivariable Cox proportional hazards model (p = 0.032 and p = 0.048, respectively). In addition, overexpression of Notch1 predicted overall survival (OS) (p = 0.018). The group with overexpression of both Notch1 and FABP7 had the shortest RFS and OS (p = 0.01 and p = 0.048, respectively). These data indicate that the poor differentiation of tracheobronchial ACC is associated with activation of Notch signaling. In the present case, the patient’s tumor was positive for FABP7 but negative for Notch1 (Fig. 4C). Three years after surgery, the patient had multiple lung metastases. This suggests that FABP7 may be a prognostic indicator of ACC.

Surgery remains a primary treatment for ACC involving the thyroid\textsuperscript{16}. The best surgical option depends on the primary tumor location, as well as the extent of tissue and organ involvement. Therefore, we did choose the best possible procedures in surgery for
individual cases. ACCT generally involves direct extension into the thyroid, and few cases exhibit metastasis. The close proximity of the trachea to the thyroid makes it difficult to determine the origin of a tumor preoperatively, which may lead to misdiagnosis.

Conclusion

We report a case of ACCT with thyroid invasion, which is an extremely rare malignant neoplasm. FNAC was useful in differentiating ATC from other diagnoses and enabling appropriate surgical treatment.

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Conflict of interest

The authors have no conflicts of interest.
References

1. Tamaki T, Dong Y, Ohno Y, et al. The burden of rare cancer in Japan: Application of the RARECARE definition. Cancer Epidemiol. 2014; 38(5): 490-495.

2. Bradley PJ. Adenoid cystic carcinoma of the head and neck: a review. Curr Opin Otolaryngol Head Neck Surg. 2004;12(2):127–32.

3. Djaković Ž, Janevski Z, Cesarec V, et al. ADENOID CYSTIC CARCINOMA OF DISTAL TRACHEA: A CASE REPORT. Acta Clin Croat. 2019; 58(4): 777-779.

4. Bhattacharyya N. Contemporary staging and prognosis for primary tracheal malignancies: a population-based analysis. Otolaryngol Head Neck Surg. 2004; 131:639–642

5. Qi D, Feng L, Li J, et al. Primary adenoid cystic carcinoma of the trachea with thyroid invasion: a case report and literature review. Onco Targets Ther. 2016; 9:6291-6296.

6. Kukwa W, Korzeń P, Wojtowicz P, et al. Tracheal adenoid cystic carcinoma mimicking a thyroid tumor: a case report. Oncol Lett. 2014;8(3):1312–1316.

7. Rocca BJ, Barone A, Ginori A, et al. Unusual presentation of metastatic adenoid cystic carcinoma: a challenge in aspiration cytology of the thyroid. Pathologica. 2014;106(4):342–344.

8. Lee MW, Batoroev YK, Odashiro AN, et al. Solitary metastatic cancer to the thyroid: a report of five cases with fine-needle aspiration cytology. Cytojournal. 2007;4:5.

9. Khademi B, Negahban S, Aledavood A, et al. An unusual thyroid mass. Am J Med. 2015;128(10):e29–e30.

10. Sondos Al K, Wafa A, Omar K, et al. Advanced Tracheal Adenoid Cystic Carcinoma with Thyroid Invasion Mimicking Thyroid Cancer Treated with Definitive Radiation: Case Report and Review of the Literature. Case Rep Oncol. 2017 Aug 4;10(2):706-712.

11. Anaplastic thyroid carcinoma in fine needle aspirates. Us-Krasovec M, Golouh R, Auersperg M, et al. Acta Cytol. 1996; 40(5):953-8.

12. Unique growth pattern in papillary carcinoma of the thyroid gland mimicking adenoid cystic carcinoma. Baloch ZW, Segal JP, Livolsi VA. 2011; Endocr Pathol.22(4):200-5.

13. Grego-Bessa J, Diez J, Timmerman L, et al. Notch and epithelial-mesenchyme transition in development and tumor progression: another turn of the screw. Cell Cycle. 2004; 3:718-21.

14. Ferrarotto R, Mitani Y, Diao L, et al. Activating NOTCH1 mutations define a distinct subgroup of patients with adenoid cystic carcinoma who have poor prognosis, propensity to bone and liver metastasis, and potential responsiveness to Notch1 inhibitors. J Clin Oncol. 2017; 35:352-60.

15. Xie M, Wu X, Zhang J, et al. The Prognostic Significance of Notch1 and Fatty Acid Binding Protein 7 (FABP7) Expression in Resected Tracheobronchial Adenoid Cystic Carcinoma: A Multicenter Retrospective Study. Cancer Res Treat. 2018 Oct;50(4):1064-1073.

16. Idowu MO, Reiter ER, Powers CN. Adenoid cystic carcinoma: a pitfall in aspiration cytology of
the thyroid. Am J Clin Pathol. 2004;121(4):551–556.
Figure legends

Fig. 1 Computed tomography scan and ultrasonography of the trachea and thyroid
(A) Computed tomography (CT) scan and (B) ultrasonography (US) of the right lobe of the thyroid. A low-density tumor with irregular edges and convexity was identified on the right side of the thyroid (white arrowhead). The images indicate submucosal invasion of the trachea with stenosis and infiltrating to the anterior surface of the cricoid cartilage.

Fig. 2 Fine needle aspiration cytology findings
Fine needle aspiration cytology (FNAC) was performed on the right lobe of the thyroid. (A) Loosely cohesive sheets and three-dimensional clusters of tumor cells against a clear background (medium power, ×400, Papanicolaou method). (B) Aggregates of small round cells surrounding light green homogeneous material (high power, ×600, Papanicolaou method). (C) Pale green globules were found in the tumor cells (high power, ×600, Papanicolaou method)

Fig. 3 Macroscopic findings after operation
(A) The entire specimen and (B) cut surface of the specimen. The tumor is located in the right posterior wall of the trachea with extension into the right thyroid gland, subglottic part of the larynx (white arrowhead).
Scale bar: 2 cm

Fig. 4 Pathological examination
(A) The tumor originating in the trachea directly infiltrated the adjacent thyroid gland (hematoxylin-eosin staining ×100, scale bar: 200 μm). (B) Tumor involvement in the surrounding soft tissue (hematoxylin-eosin staining ×400, scale bar: 50 μm). (C) Immunohistochemical expression of FABP7 was apparent (immunohistochemistry ×200; scale bar: 100 μm).
Fig. 1
Computed Tomography scan and Ultrasonography of the trachea and thyroid
Fig. 2
Fine Needle Aspiration Cytology findings
Fig. 3

Macroscopic findings after operation
Fig. 4
Pathological examination