—Case Reports—

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). Tracheal origin was confirmed postoperatively.

Case Description: A 77-year-old woman presented to our hospital with acute inspiratory dyspnea requiring emergency tracheotomy. Physical examination revealed swelling of the right anterior neck and a hard, immobile 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. We performed FNAC. Clinical findings were highly suggestive of ACCT with thyroid invasion. She underwent total laryngectomy, cervical esophagectomy, and thyroidectomy with bilateral selective neck dissection at another hospital. The tumor was located in the right posterior wall of the trachea and extended into the right thyroid gland. Pathological examination showed 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 positive for FABP7, a putative prognostic marker of ACC, and metastasized to the lungs 3 years after 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.

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Key words: fine-needle aspiration cytology, adenoid cystic carcinoma, adenoid cystic carcinoma of the trachea, anaplastic thyroid carcinoma, fatty acid binding protein 7

Introduction

Adenoid cystic carcinoma (ACC) is a rare cancer; annual incidence is less than 6 per 100,000 population[1]. ACC was first described as cylindroma by Billroth in 1853, and its current name was proposed by Spies in 1930[2]. ACC is categorized into 3 subtypes. The cribriform pattern is most common, the tubular form has a good prognosis, and the solid form is associated with poor outcomes.

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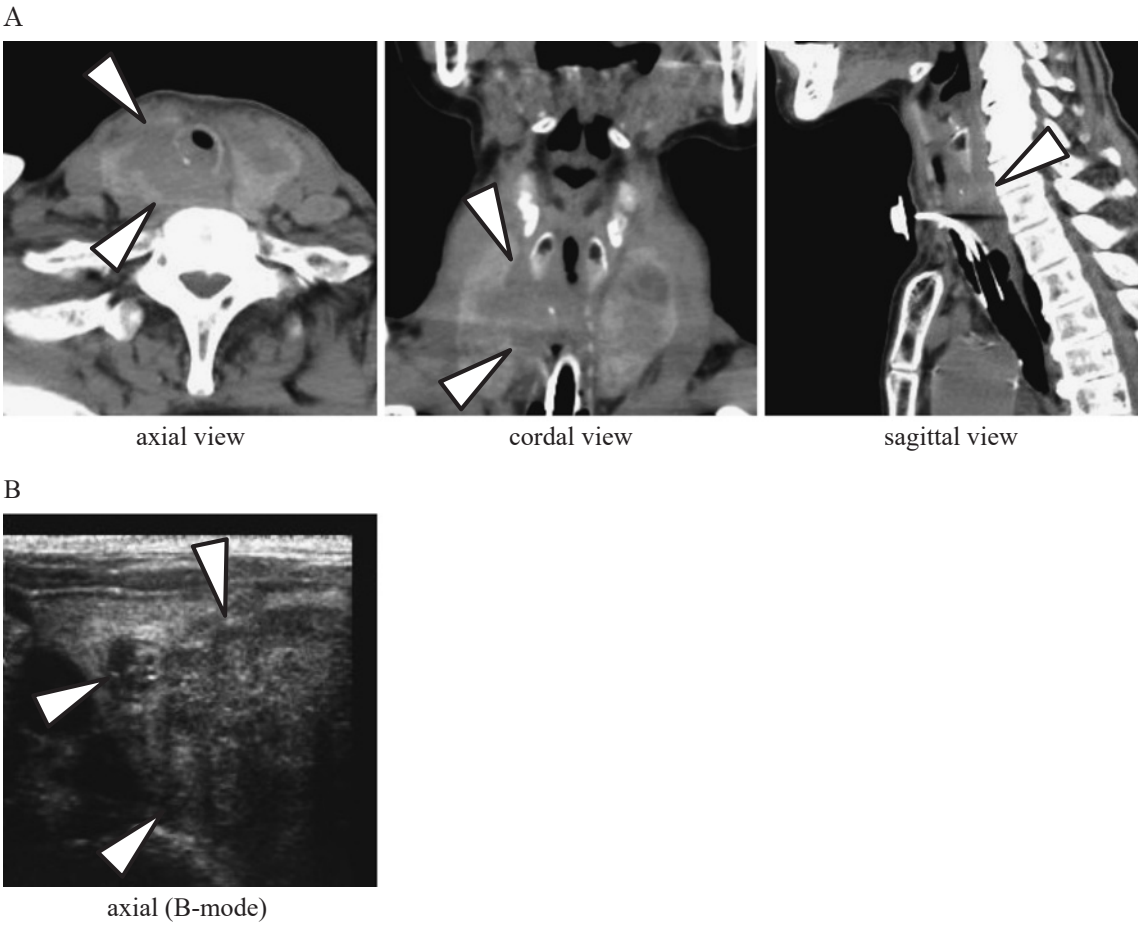

Fig. 1 Computed tomography scans and ultrasonogram of the trachea and thyroid
(A) Computed tomography (CT) scans and (B) an ultrasonogram (US) of the right lobe of the thyroid. A low-density tumor with irregular edges and convexity was identified on the right side of the thyroid (white arrowhead). The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

ACC of the trachea (ACCT) is rare, with an overall annual incidence of less than 0.2 per million[3], and ACCT with thyroid invasion is extremely rare. The predominant clinical symptoms of ACCT are dyspnea and hoarseness, and the tumor is a 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 and was diagnosed in fewer than 2% of patients with thyroid carcinomas. Some patients with ATC present with acute respiratory symptoms because of tracheal invasion.

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

We initially suspected ATC in our patient. The original site of the tumor could not be identified during paraclinical investigation. After emergency tracheotomy because of acute inspiratory dyspnea, we conducted FNAC and diagnosed ACC. The tracheal origin of the tumor was confirmed only after pathological examination and diagnosis of the operative specimen. This report describes a case of ACCT that extended into the thyroid gland, which resembled ATC on imaginig 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 a thyroid clinic with acute inspiratory dyspnea requiring emergency tracheotomy. She reported hoarseness of 4 months' duration.

Physical examination revealed right anterior neck swelling with a hard, immobile mass. Laboratory tests showed that blood levels of thyroid hormones (fT4: 1.3

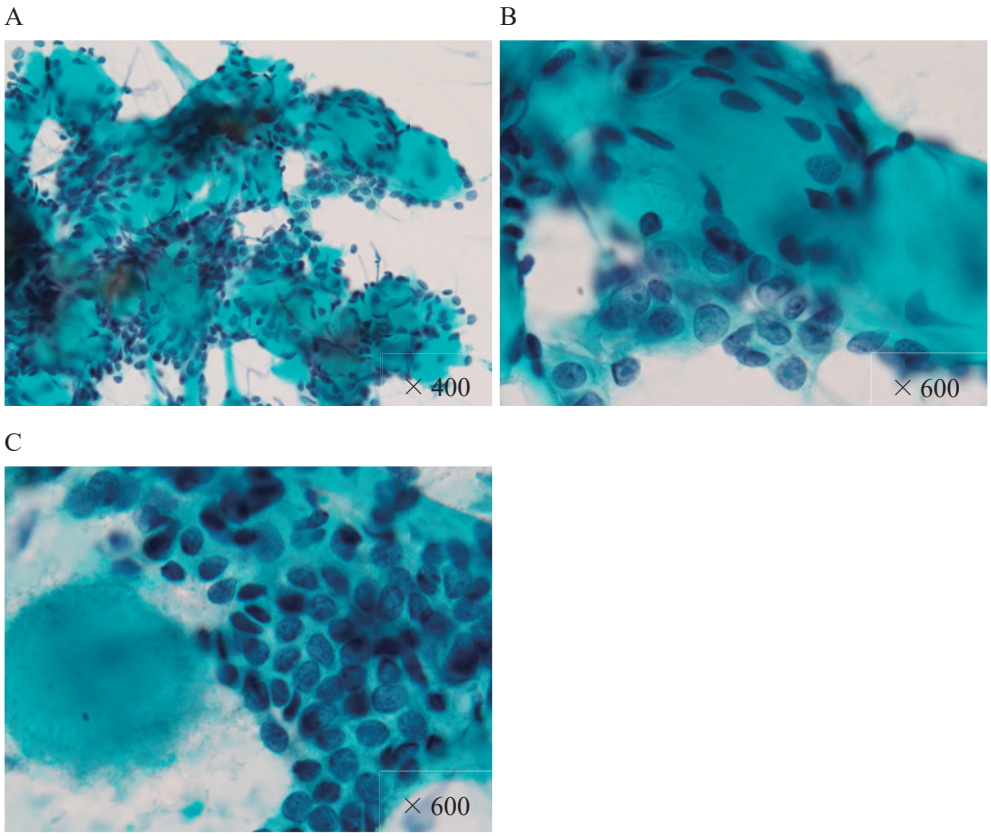

Fig. 2 Fine-needle aspiration cytology findings
Fine-needle aspiration cytology (FNAC) of the right lobe of the thyroid was performed. (A) Loosely cohesive sheets and three-dimensional clusters of tumor cells against a clear background (medium power, ×400, Papanicolaou method). (B) Aggregates of small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

ng/dL, fT3: 2.9 pg/mL, TSH: 1.45 μIU/mL), carcinoembryonic antigen (3.6 ng/mL), and calcitonin (1.8 pg/mL) were within normal ranges. 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 or 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, we observed aggregates of small round cells surrounding light green homogeneous material (**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 suggested ACC. No other characteristics indicative of ATC or other thyroid carcinomas were observed. Medullary carcinoma was excluded on the basis of blood data. Clinical findings strongly suggested invasion of ACCT into the thyroid gland rather than tracheal invasion by thyroid carcinoma.

Because the lesion had spread to the trachea, thyroid gland, and cervical esophagus, pharyngo-laryngo-esophagectomy appeared to be indicated and the patient was referred to a hospital specializing in head and neck cancer, where she underwent total pharyngo-laryngo-esophagectomy and thyroidectomy with bilateral selective neck dissection (level II-IV). Macroscopic observation 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 third tracheal ring, and extended to the right thyroid gland. The tumor measured 5.3 × 3.2 × 2.8 cm. Pathological examination showed that it originated from the trachea, that it had di-

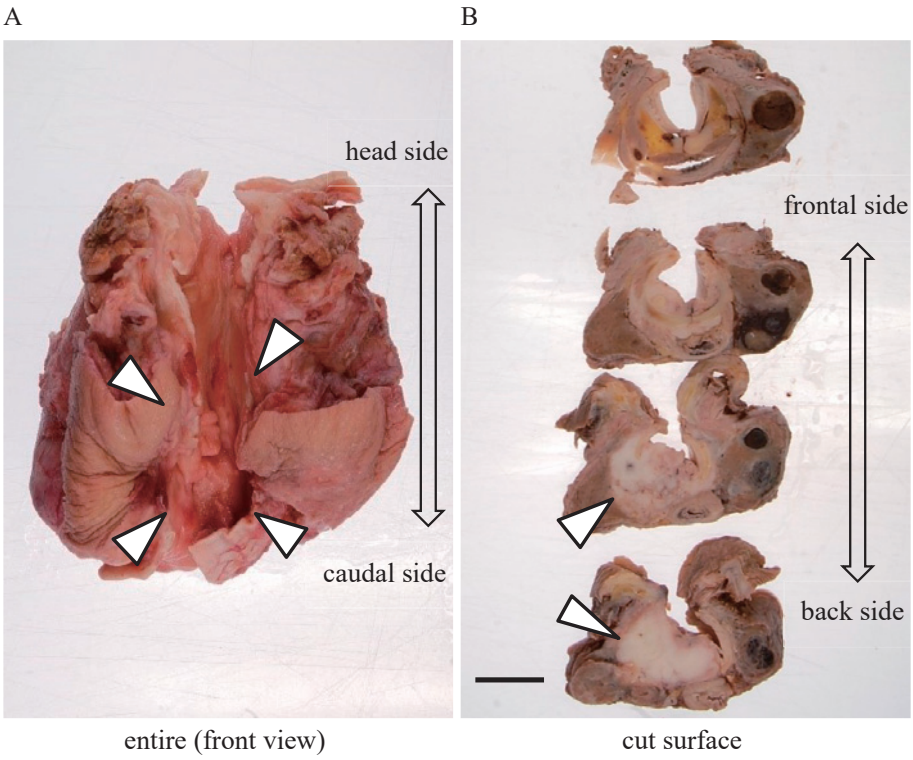

Fig. 3 Postoperative macroscopic findings
(A) The entire specimen and (B) cut surface of the specimen. The tumor was located in the right posterior wall of the trachea and extended into the right thyroid gland and subglottic part of the larynx (white arrowhead).
Scale bar: 2 cm

rectly 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[4] 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 yielded a definitive diagnosis of ACCT. Three years after surgery, lung metastases were observed.

Discussion

We report a rare case of thyroid-invading ACCT resembling ATC on FNAC in a 77-year-old woman. To date, only 10 cases of primary ACC with thyroid invasion have been reported[5]. Approximately one-third of patients with ACC develop distant metastases to common sites, such as lung, brain, bone, and liver. Of these 10 cases, the primary tumor originated in the trachea (n = 6), laryngeal minor salivary gland (n = 3), and left parotid (n = 1). These 6 patients included 2 males and 4 females (average age, 49 years; range, 17 to 68 years). The age of the oldest patient, 68 years, is highly unusual for an ACCT diagnosis. The clinical presentations consisted primarily of respiratory symptoms, such as asthma, cough, dyspnea, hoarseness, hemoptysis, wheezing, and neck pain. Three of the 6 patients had multiple organ involvement, rather than involvement of the trachea only, and 5 underwent surgical treatment. FNAC was performed preoperatively for 4 of the 10 cases, which were diagnosed as ACC[6–9]. Radiotherapy was administered in 5 patients and chemotherapy in the remaining patient, who received no additional locoregional treatment, such as irradiation, because of the patient's advanced age.

In the present patient, a CT scan showed the thyroid and tracheal masses but failed to show the relationship

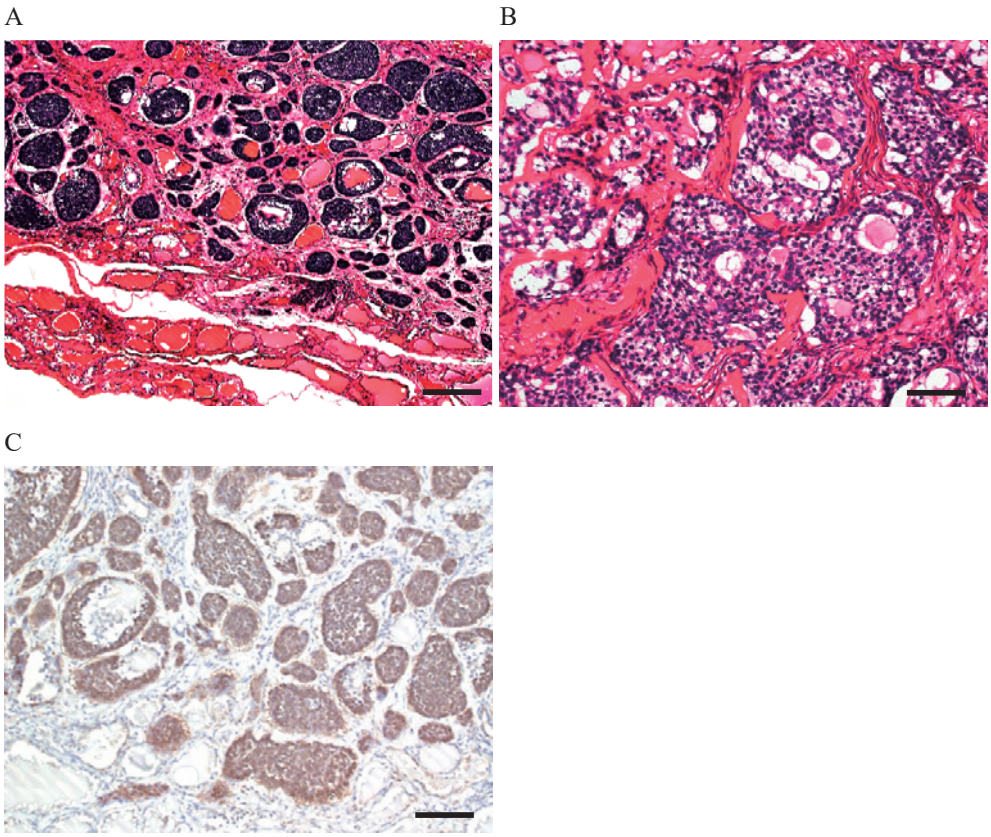

Fig. 4 Pathological findings
(A) The tumor originating in the trachea directly infiltrated the adjacent thyroid gland (hematoxylin-eosin staining ×100, scale bar: 200 μm). (B) Tumor involvement in the surrounding soft tissue (hematoxylin-eosin staining ×400, scale bar: 50 μm). (C) Immunohistochemical expression of FABP7 was apparent (immunohistochemistry ×200; scale bar: 100 μm).

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[10]. FNAC is useful for differentiating the two because diagnosis of ACC and ATC by FNAC is usually easy. However, in the case of ATC, the quality of samples is sometimes inadequate for FNAC sampling, mainly because of (1) tumor regressive changes (necrosis, hemorrhage, leukocytic infiltration), (2) extensive tumor fibrosis, and (3) distinct differentiated and anaplastic patterns in the same tumor[11]. In addition, immunohistochemistry may be necessary for accurate cytopathological and histopathological diagnosis[12]. 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, to facilitate earlier diagnosis, we suggest that a CT scan and FNAC should be completed preoperatively in cases of this type.

ACCT is very rare, but new genetic findings have been reported in recent studies. 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[13]. Ferrarotto at al.[14] found that most 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[15] reported that Notch1 and FABP7 were overexpressed in 37.8% and 38.3% of 368 patients with tracheobronchial ACC. 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 poorly differentiated tracheobronchial ACC is associated with activation of Notch signaling. In the present patient, the 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[16]. Because the best surgical option depends on the primary tumor location, as well as the extent of tissue and organ involvement, surgical procedures must be individualized. ACCT generally involves direct extension into the thyroid, and some patients develop metastases[8]. 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 described a case of ACCT with thyroid invasion, which is an extremely rare malignant neoplasm. FNAC was useful in differentiating ACC from other diagnoses and enabling appropriate surgical treatment.

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Conflict of Interest: None declared.

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