



Unusual Metastatic Presentation of Submandibular Gland Adenoid Cystic Carcinoma to the Lung, Diagnosed by Fine-Needle Aspiration Cytology: Case Report and Review of the Literature

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Abstract

Adenoid cystic carcinoma is a rare malignancy involving exocrine mucus glands, typically presenting in the salivary glands of the head and neck, but also as a primary lung neoplasm. The intention of this report is to provide more insight to adenoid cystic carcinoma due to its rarity. We present a case of a 50-year-old non-smoking Hispanic man presenting with shortness of breath and the presence of lung nodules on imaging. Biopsy of one of the Lung nodules proved to be metastatic adenoid cystic carcinoma originating from a prior adenoid cystic carcinoma from the right submandibular gland. This case report discusses the diagnosis of metastatic Adenoid Cystic Carcinoma utilizing cytology samples obtained by Fine Needle Aspiration alone, without the need for surgical biopsy. We review the histological presentation, demographics, molecular basis, metastasis, and treatment of adenoid cystic carcinoma.

Keywords: Metastasis; Adenoid cystic; Cytopathology; Fine needle aspiration; Recurrence

Abbreviations

ACC: Adenoid cystic carcinoma; **FNAC:** Fine Needle Aspiration Cytology; **IHC:** Immunohistochemistry

Introduction

Adenoid cystic carcinoma (ACC) is an uncommon epithelial malignancy of the salivary glands. Approximately 1 out of 10 neoplasms of the salivary gland are an ACC [10]. ACC consists of three different presentation: tubular, cribriform, and solid types, but it often presents as a mixture of the three architectural patterns [7]. The typical presentation of ACC is the cribriform type, but the solid morphology has the most aggressive clinical course because it is significantly associated with distant metastasis [7,12]. ACC typically shows infiltrative growth and perineural invasion. It usually metastasizes to the lungs, bones, liver, and brain [4,11]. Noor et al. also reported renal and skin metastasis [4]. ACC has an indolent clinical course and delayed

recurrence with possible metastasis even several years after initial treatment [1,4]. Therefore, it is adamant to follow-up with long term care for patients with ACC [1,4]. Different variables also contribute to the clinical course of ACC. Variables include: Location of origin [1,12], patient's age [1], and molecular expressions [6,27]. In our patient's case, we used Fine Needle Aspiration Cytology (FNAC) with sufficient samples to generate a cellblock, which was used for immunohistochemistry studies (IHC). The combination of cytology and radiology has allowed for minimally invasive, safe, accurate, and cost-effective diagnosis of suspicious masses, previously accessible only by surgical biopsy techniques. As a result, cytologists are increasingly called upon to diagnose disease in a specimen procured under image guidance for different organs. Rather than causing delay, cytology facilitates timely diagnosis and management, and it is an integral part of a multimodal approach to various tumor diagnoses. On site cytology interpretation increases the diagnostic yield of the procedure by allowing for additional needle passes as necessary [16].

The primary role of using FNAC in salivary gland lesions is to differentiate between benign and malignant lesions and to determine the plan of surgical excision [24]. Here, we report the uncommon presentation of this case of metastatic adenoid cystic carcinoma to the lung originating from a prior adenoid cystic carcinoma from the right submandibular gland.

Case Presentation

A 50-year-old Hispanic man with no smoking history presented with shortness of breath, and imaging studies demonstrated 3 lung nodules, the largest measuring 3.4 × 2.9 cm. The possibility of metastatic disease versus multifocal primary lung cancer was raised. Fine-needle aspiration biopsy of one of the lung nodules

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showed small, monotonous basaloid cells with scant cytoplasm, and naked, stripped nuclei. The cells were also arranged in pseudoglandular clusters and as small sheets surrounding metachromatic hyaline material with isolated mitoses. Necrosis was absent. In addition, the cytomorphologic examination revealed tight, globular, honey-comb arrangements of cells lacking true nuclear molding; and presence of acellular portions of basal lamina material. Perineural invasion, characteristic of ACC was prominent in several foci of the examined cellblock [Figure 1 A-B-C-D B]. The differential diagnosis included a basal cell neoplasm; low-grade polymorphous adenocarcinoma; mucoepidermoid carcinoma; and less likely, a primary lung carcinoma including primary ACC. The striking cytomorphologic characteristics of the cytology smears prompted “directed” history, and the patient reported a remote history of adenoid cystic carcinoma [ACC] of the right submandibular gland twelve years prior to current presentation. It was surgically removed with no post-operative therapy. Correlative review of the primary salivary gland tumor and current cytology showed similar cytomorphology allowing the diagnosis of metastatic ACC to the lung. To distinguish primary ACC of the lung from metastatic ACC to the lung, Immunomarker TTF-1 was utilized showing negative staining in support of metastatic ACC. In addition, the tumor cells were positive for c-KIT(CD117) in support of the diagnosis.

Patient was offered surgical treatment with lung nodules metastasectomy, however, he refused additional surgery and decided to proceed with chemoembolization and radiofrequency ablation. Despite this treatment, he showed disease progression with development of recurrent lung nodules 7 months post treatment. Non-surgical treatment continued, patient was free of recurrence or additional metastasis for 2 years, after which he was lost to follow up.

Discussion

ACC is rare and comprises approximately 1% of the malignancies in the head and neck region [10]. It encompasses only 15-20% of all salivary gland malignancies, most of which occur in the minor salivary glands [28]. Even though ACC is classified with salivary gland tumors, it originates from the exocrine mucous glands, because of this, it can occur at any place in the body where mucous glands are present [28]. ACC is most often found in younger and middle-aged adults, but it can occur in any age, including children. ACC is found mostly in women with an approximately 60% of all cases being females [28, 17]. Slow local growth with local spread and perineural invasion are the hallmarks of this entity, rendering metastasis to the lung an unlikely and uncommon presentation.

Prognosis can vary depending on the location of the primary site. Studies revealed that lower survival rates are associated with patients when the tumors are located in the tongue, hard palate, and sino-nasal tract, compared to tumors originating from the parotid, submandibular gland, buccal region, base of the tongue, and soft palate which have a better prognosis [1,12]. Ouyang et al. reported that older patients are more likely to present with late-stage tumors and are more prone to recurrence and distal metastasis. ACC patients with those risk factors should be more carefully managed during treatment and follow-up visits.

Among the three types of ACC, the solid type has significant overlap with a large range of neoplasms morphologically, including other carcinomas and sarcomas [29]. Thus, immunohistochemistry is often necessary to confirm the diagnosis of ACC. Expression of a receptor tyrosine kinase, c-KIT(CD117) and Myb, is commonly detected by immunohistochemistry in

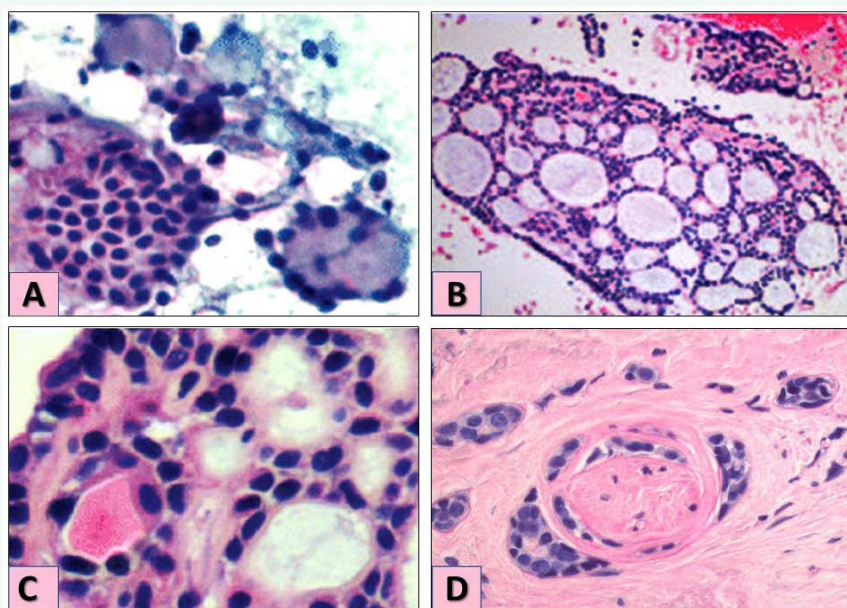


Figure 1 Cytomorphologic examination, FNA of lung nodule. **1A:** The cells are arranged in pseudoglandular clusters (Papanicolaou stain X40). **1B:** Tight, globular, honey-comb arrangements of cells giving a cribriform architecture (H&E stain X40). **1C:** Clusters and small sheets surrounding metachromatic hyaline material (H&E stain X60). **1D:** Prominent perineural invasion (Cellblock H&E stain X40).



ACC cell [27]. Among salivary gland tumors, Myb overexpression is highly specific for ACC [6]. Myb is considered an oncogene, which is involved in cellular differentiation and proliferation [5]. The *MYB* locus (on chr. 6) can undergo translocation with the *NF1B* locus (on chr.9), and this *MYB-NF1B* t (6;9) (q22-23; p23-24) translocation is a molecular hallmark of ACC, found in over 50% of cases [30]. Park et al. suggest that Myb positive patients have a diminished risk of distant metastasis [6]. In our presented case, the striking cytomorphologic and histomorphologic similarity of both primary and metastatic tumors was sufficient to render the final diagnosis without the need of using ancillary studies. However, TTF-1 immuno marker was utilized to differentiate primary lung ACC from metastatic ACC. The tumor was negative for TTF-1 in support of metastatic ACC. In addition, the tumor cells were positive for c-KIT (CD117) in support of the diagnosis.

About 40% of patients with ACC develop metastatic disease [26]. De Mendonc et al. suggests that NOTCH1 (a disintegrin), ADAM-12 (metalloproteinase 12), HIF-1 α (a hypoxia-inducible factor), and HB-EFG (a heparin-binding epidermal growth factor) are all factors that are directly related to ACC's mechanism of invasion and subsequent metastasis. These factors are most likely components of the cell signaling pathway observed during malignancy related hypoxia, which subsequently can lead to enhanced invadopodium formation. Invadopodium are structures responsible for the degradation of the extracellular matrix seen in cancer invasion and metastasis [9]. In addition to the hypoxia related protein (HIF-1 α), Oplatek et al. also highlighted that lymphovascular invasion is strongly associated with decreased survival [31]. Patients with regional cervical lymph node metastasis lived, on average, 52 months less than those without evidence of regional metastasis [31]. Therefore, once a patient is found to have lymphovascular involvement, close monitoring and periodical chest radiographs for detecting distal metastasis should be strictly implemented [1]. To determine the risk factors of potential distant metastatic development and chances of survival, Bhayani et al. retrospectively reviewed 60 patients who were diagnosed with ACC at an early clinical stage (T1-2/N0, stage 1 tumor that has not spread to the lymph nodes or other parts of the body) [12]. Distant metastasis was associated with ages ≥ 45 years old, extracapsular spread from lymph nodes, high-grade histology, and solid tumor subtype of ACC [12].

In addition to the aforementioned locations, ACC can infrequently occur as a primary tumor of the lung, which is why it can be mistakenly thought to be small cell carcinoma of the lung or other primary lung neoplasms [3]. According to Bhattacharyya et al., ACC's primary location can be established in the lung due to the presence of tracheobronchial glands distributed throughout airway submucosa. It can also present morphologically similar to the three types mentioned previously of ACC [3]. If ACC presents in the peripheral lung, a differential must be made to distinguish ACC from other metastatic tumors of the lung. For this purpose, immunostaining for TTF-1 is useful to diagnose a lung primary lesion [14]. The reason this method can be implemented is because TTF-1 is a transcription factor expressed specifically in the thyroid [in follicular epithelial cells] and lungs [in type

II pneumocytes and Clara cells]. Additionally, it was noted by Berghmans et al., that TTF-1 is also expressed in pulmonary adenocarcinomas 60-70% of the time [14]. However, TTF-1 is not expressed in metastatic lung tumors with the exception of thyroid metastatic tumors [2,14,15]. Because of this, TTF-1 is a useful marker to distinguish between metastatic lesions and primary lung lesions [2,14,15].

In cytology specimens, ACC is recognized by the presence of basaloid cells and a homogenous matrix material, both of which are considered cornerstones for recognition [16]. However, it can be challenging to differentiate adenoid cystic carcinoma from other more common entities of the lung, such as primary small-cell neoplasms. A study by Anderson et al. compared the cytomorphology of adenoid cystic carcinoma with well-differentiated adenocarcinoma, small-cell undifferentiated carcinoma, and carcinoid tumor of the lung. They suggested that the differential features distinguishing ACC from the other lung neoplasms include: the tight, globular, honey-comb arrangements of cells which lack true nuclear molding; acellular portions of basal lamina material, which alone suggest possible ACC; the extension of a solid core of basal lamina past a sieve-like cellular meshwork [24]. Based on these criteria, the morphologic expression of metastatic adenoid cystic carcinoma is distinguished from other lung entities and permits a definitive diagnosis [24].

Surgical excision of localized tumor is considered the first line of management for primary salivary gland neoplasms [20]. Surgery is considered the most successful if the margin removed during surgery is found to be "clean,". This means the tumors should be managed with minimum of 2 millimeters of cancer-free tissue surrounding the tumor [20,23]. In our reported case, the status of the surgical margins of the excision of the primary tumor was not reported, and margin involvement cannot be ruled out. However, treatment of disseminated ACC is challenging; there is currently no consensus about the optimal therapeutic approach. There is debate even on the role of surgery, since it might not necessarily increase survival. Often ACC is unresponsive to chemotherapy; however, palliative chemotherapy might be used in symptomatic patients, with various responses, which might not necessarily be attributed to chemotherapy itself but rather to the indolent clinical evolution of ACC [32].

One of the options to treat metastatic ACC is metastasectomy with surgical removal of all metastatic nodules if surgically feasible. In the Girelli et al study, there were 109 cases of ACC coupled with a lung metastasectomy and disease-free intervals reported greater than 36 months post treatment [25]. Additionally, it was noted that the best prognosis was seen with completeness of resection with lung metastasectomy [25]. In our reported case, patient refused additional surgery and decided to proceed with chemoembolization and radiofrequency ablation. Patients with recurrent ACC or patients that present with metastasis are considered generally inoperable, but occasionally metastasectomy can be offered [20]. For primary ACC, in addition to surgery, postoperative radiation therapy is also associated with an improved outcome [13]. According to Lee et al., 5-year survival was 72.5% for those receiving surgery alone compared to 82.4% for those receiving postoperative radiation [33]. Primary



treatment with radiation should be considered as an alternative treatment, if surgery is not possible [23]. The ionizing radiation causes the salivary glands to undergo structural degradation and the eventual death of the affected cells [21,23]. Atri et al found that dose tolerance of the salivary glands varied between 32 Gy (Gray-the ion radiation unit) and 46 Gy [22,23]. However, the curative dose of head and neck tumors may rise to 60 Gy or more [22,23]. This value is more than the dose tolerance range of the salivary glands. If the salivary glands are exposed to more than their tolerance range, it may lead to permanent injury and dysfunction and subsequently cause xerostomia [22,23].

Currently there is limited evidence, but it was observed that superselective intra-arterial cisplatin infusion with concomitant radiotherapy is also a promising treatment, achieving an 80% complete response rate in advanced cases of carcinoma in the head and neck [18,19]. The treatment involves infusing cisplatin directly into the tumor bed, which minimize the effects of the drug systemically [18,19]. This line of treatment was attempted with our patient. However, evidentiary support about the use of chemotherapy agents, conventional cytotoxic agents, and targeted therapies currently are still lacking [8]. One of the main constraints in obtaining data pertaining to ACC is the rarity of this neoplasm which makes the conductance of a well-designed clinical trial logistically challenging [8]. Considering ACC has a tendency for delayed recurrence and possible metastasis even several years after initial treatment [1,4], long-term follow up is adamant [7].

It is our hope that this report raises awareness of what remains an unmet need in the knowledge of diagnosis and management of “metastatic adenoid cystic carcinoma.” Hopefully, continued investigation drives further development of efficacious diagnosis and safe treatments for improving patient outcomes.

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