Case Report

Malignant Pleural Effusion, an Unusual Presentation of Metastatic Adenoid Cystic Carcinoma: A Case Report and Review of the Literature

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Adenoid cystic carcinoma (ACC) is an uncommon malignant neoplasm of the major and minor salivary glands that is known to have a long clinical course, behaving in an insidious and indolent fashion with multiple recurrences preceding distant metastasis. Reported here is a case of a patient presenting with shortness of breath and recurrent pleural effusion. Exfoliated ACC cells were observed on cytological evaluation, a rare occurrence. Mediastinal lymph node involvement was also confirmed on cytology. A primary site of origin was not found. In summary ACC can present in various body sites and pathologists should consider ACC in the differential diagnosis of a basaloid carcinoma of uncertain origin.
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INTRODUCTION

Adenoid Cystic carcinoma is a rare epithelial tumor of the salivary glands that was first described by Billroth as "Cylindroma" in 1859.[1] Primary ACC can arise from any organ where seromucinous or sweat gland epithelium is present.[2] These are found in structures derived from the foregut,[3] that is the parotid, submandibular and sublingual glands and the mucus glands and lacrimal glands throughout the upper respiratory tract, tracheobronchial tree,[4,5] lung,[6,7] skin, breast,[2.8.9] and uterine cervix.[2,7] It accounts for 5% to 10% of all salivary gland tumors and accounts for 1% of all head and neck malignancies. Among the major salivary glands, the parotid gland is the most common site of occurrence.[8] Approximately 50% of intraoral ACC's occur on the palate,[10] with nose and paranasal sinuses also common sites of occurrence.[8]

Adenoid cystic carcinoma is a morphologically distinctive malignant neoplasm[7] with biologic features of perineural spread,[10] an indolent but persistent and recurrent growth pattern, long clinical course and late onset of metastases.[7,8] The peak incidence is in the fifth to sixth decade[10] and patients with major salivary gland ACC present, on average, a decade earlier than patients with minor salivary gland tumors.[8] Incidence in females is slightly higher than males.[8,10] Histologically, ACC may show three different growth patterns: glandular (cribriform), tubular and solid[11] with the cribriform subtype having the best prognosis and the solid subtype the worst,[8,10] showing a higher incidence of metastasis.[12] Distant hematogenous metastasis, particularly to the lung[13] but also to bone, brain and liver[5,8] have been reported many years after the primary tumor is discovered[13] and is far more frequent than regional lymph node metastasis.[8,13]

Reported below is a case of malignant pleural effusion with exfoliated ACC cells, and positive ipsilateral paratracheal (4R) lymph node, a rare presentation that to the author's knowledge has not been reported previously.

CASE REPORT

A 77-year-old male with a past history of coronary artery disease with coronary artery bypass grafting, presented with shortness of breath on exertion. He was a nonsmoker but reported occupational exposure to asbestos (worked in the navy for 6 years and steel factory >10 years). Thoracic CT showed a large right pleural effusion, old granulomatous disease and areas of atelectasis in the right lung related to pleural effusion, thereby making it difficult to exclude endobronchial lesions. All other systems were negative. Cytology results of pleural fluid were reported as suspicious for epithelial malignancy, possible etiologies being well differentiated squamous cell carcinoma, salivary gland neoplasms or reactive. The patient was followed by pulmonology for recurrent pleural effusions and was again sent to interventional radiology for therapeutic and diagnostic thoracentesis. Both effusions were exudative with lymphocytic predominance.

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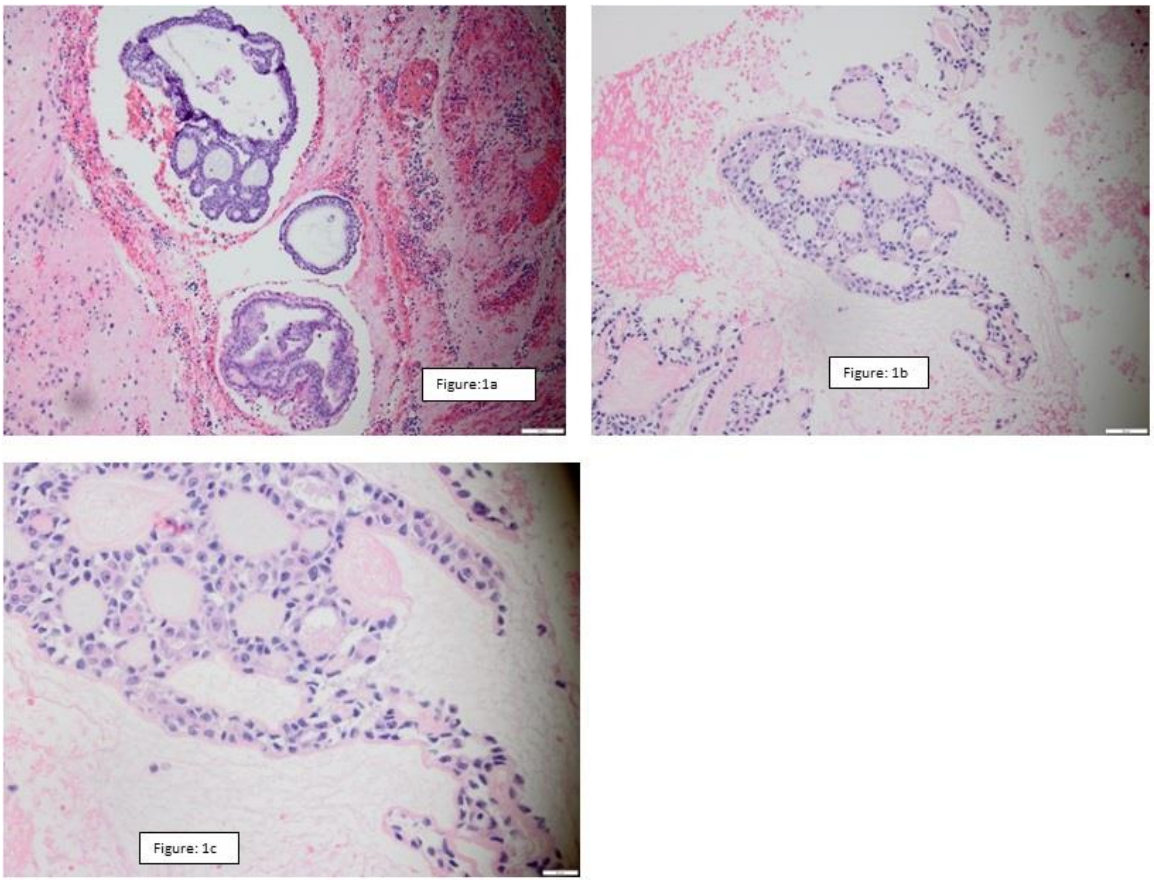

Figure 1. 1a: Pleural fluid cell block showing complex gland like spaces lined by a dual layer of hyperchromatic cells. Background of mesothelial cells lymphocytes, histiocytes and blood. (H&E x 20). **1b:** Cell block of lymph node FNA showing tumor with Cribriform pattern characterized by nests of tumor cells containing sharply outlined luminal spaces with mucin like secretions. The dual population of cells includes myo-epithelial cells with scant cytoplasm and hyperchromatic angulated nuclei and the ductal cells with more abundant eosinophilic cytoplasm with paler nuclei and visible nucleoli. homogenous eosinophilic material can be seen surrounding the cribriform structure. (H&E x 20). **1c:** Same field as 1b at x 40 magnification.

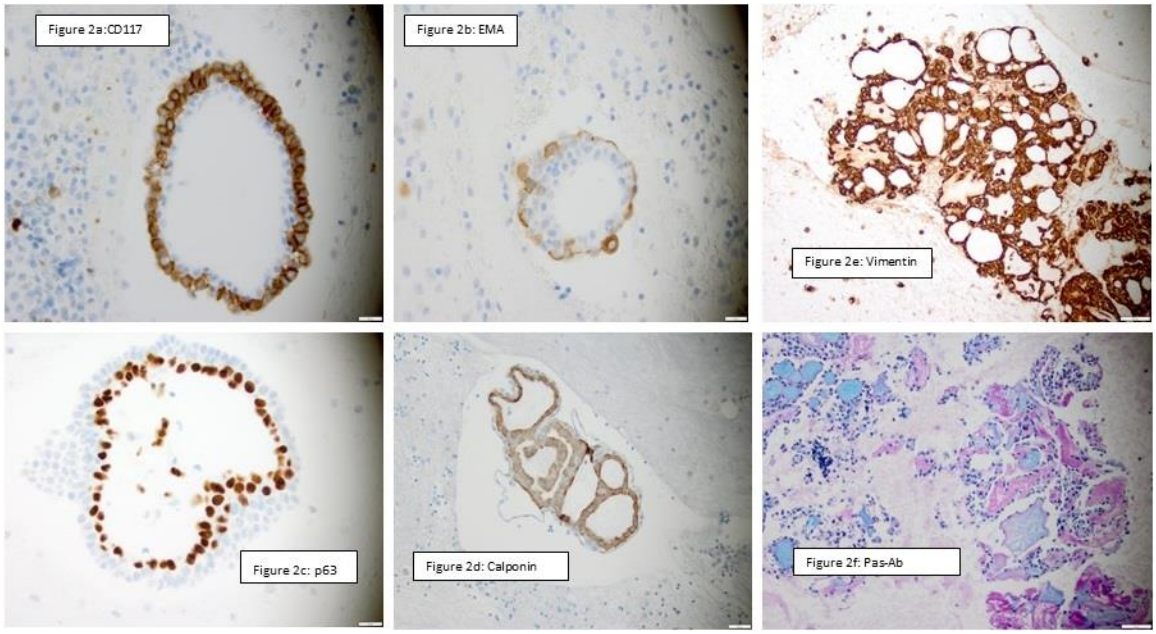

Figure 2. 2a, 2b: Ductal cells are positive for CD117 and EMA. **2c, 2d:** Myo-epithelial cells are positive for p63 and Calponin. **2e:** Tumor cells are positive for Vimentin. **2f:** Basement membrane like material surrounding cylindrical spaces is PAS positive while Alcian blue stains the mucoid material within the spaces. (**2a-2c**: x20; **2d-2f**: x10).

The second pleural effusion cytology specimen showed metastatic carcinoma having myoepithelial features. The myoepithelial nature of the basal cells was confirmed by Calponin, p63 and smooth muscle myosin IHC stains. Tumor cells also stained positive for p40. The adluminal cells were positive for CD117 and EMA. The immunophenotypic profile of IHC stains performed on this specimen favored adenoid cystic carcinoma or other salivary gland carcinoma with myoepithelial features over the previously favored squamous cell carcinoma. The presentation of malignant effusion was noted as unusual for these indolent low grade tumors when arising in head and neck, and a search for the likely primary origin in minor salivary glands associated with the tracheobronchial tree was recommended **(Figures: 1a, 2a-2f)**.

The patient's pleural effusion and shortness of breath recurred and he was admitted for pleurex catheter placement. A follow-up CT of the thorax showed small bilateral pulmonary and subpleural nodules measuring up to 0.8 cm, worrisome for metastatic disease. In addition, right hemithorax pleural nodularity and mediastinal adenopathy compatible with metastatic disease were noted along with patchy consolidation in the right lower and right middle lobes, worrisome for superimposed infection (**Figure 3a**).

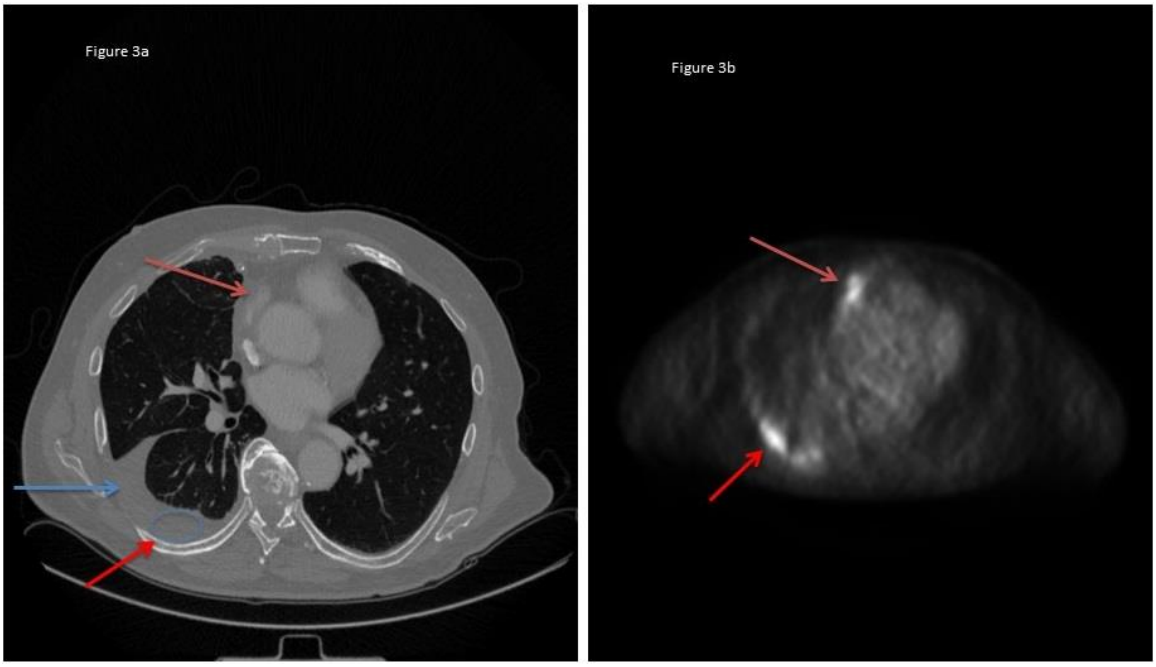

Figure 3. 3a: Enhanced CT scan shows right hemithorax subpleural tumor (red arrow) associated pleural effusion (blue arrow) and enlarged right hilar lymph nodes. (orange arrow). **3b:** PET image shows areas of enhanced 18 F-FDG uptakes corresponding to the right subpleural mass and effusion (red arrow) and right hilar lymphadenopathy (orange arrow).

A subsequent PET scan showed hypermetabolic pleural nodularity in the right posterior lung field accompanied by hypermetabolic right hilar and mediastinal lymphadenopathy, consistent with malignancy. A hypermetabolic small right pleural effusion and other areas of hypermetabolic activity along the right pleura were noted consistent with a malignant pleural effusion. Hypermetabolic patchy increased density in the right middle lobe felt to represent resolving infection was also noted along with postsurgical changes from CABG **(Figure 3b).**

An endobronchial ultrasound guided fine needle aspiration of the 4R lymph node was performed. The final pathologic results were reported as adenoid cystic carcinoma, with the note that these carcinomas usually arise within salivary glands (major or minor), but can rarely arise at other sites, including lung, breast & skin. This case was compared with its two pleural fluid cytology predecessors, all showed essentially identical histological features **(Figure 1b, 1c)**.

The patient began a course of radiation treatment for metastatic adenoid cystic carcinoma with mediastinal nodal disease and malignant pleural effusion. Palliative RT was used to optimize local control of the bulky right chest lesion.

The patient's right lung bulky disease was treated with conformal radiation treatment with dynamic multi-leaf collimation. The target received 3750 cGy at 250 cGy per fraction in 15 fractions. 6 MV photon was used. The patient tolerated radiotherapy without significant side effects.

He has finished the radiation to his mediastinum and right pleura. His catheter was no longer draining fluid and was therefore removed. He was having no breathing difficulty and

his appetite and weight are currently stable. Currently he is well and is on active surveillance.

DISCUSSION

Primary Salivary gland-type lung cancers are rare[14] and represent about 0.04-0.2% of all lung cancers.[7] The majority arise from the tracheobronchial glands and therefore greater than 90% arise in the central bronchi rather than in the segmental bronchi,[5,6,9] hence reports of adenoid cystic carcinoma originating in the peripheral lung are rare. In cases of occurrence in the periphery, lung metastasis from a primary salivary gland tumor must be ruled out.[6,9]

Several clinicopathologic factors associated with poor prognosis have been suggested including histologic grade, distant metastasis and local recurrence.[15] Histopathologic evaluation is essential for differentiating adenoid cystic carcinoma from other pulmonary lesions[14] and for grading the tumor. Three recognized histopathologic patterns of ACC are cribriform, tubular and solid, with the cribriform pattern being the commonest and easily recognizable, and the solid the least common pattern. The cribriform pattern is thought to have the best prognosis and the solid subtype the worst,[12,13] with the tubular form possessing an intermediate prognosis,[8] in terms of recurrence rates, distant metastases and overall survival.[3] More than one subtype maybe seen in the same tumor and the predominantly cribriform and tubular are graded as grade 1, less than 30% solid as grade 2 and greater than 30% solid as grade 3.[3,16] All subtypes have the dual cell population of myo-epithelial cells and ductal cells.[8] Some studies have ascribed greater emphasis on the morphologic features of the lesions whereas others contend that clinical staging represents a more reliable predictor of prognosis.[7,17,18] Additionally, adenoid cystic carcinoma of the minor salivary glands is reported to have a worse prognosis than of the major salivary glands,[3,8] with a strong positive correlation with location of minor salivary gland and prognosis, most likely attributed to discovery of neoplasm after significant local dissemination and perineural spread and its poor accessibility.[3,11]

Adenoid Cystic carcinoma is a rare indolent primary tumor[9] that occurs in all age groups. There is equal sex distribution when it occurs in the airways.[9,19] A protracted course of many years with multiple local recurrences and late hematogenous metastasis is the usual clinical course for this slow growing neoplasm.[2] The commonest site of hematogenous metastasis is the lung,[1,11] for both major and minor salivary gland ACC followed by liver[1] and bone.[19] Survival of patients developing distant metastasis is significantly associated with site of metastatization and is better with lung involvement compared with bony dissemination.[17] Due to the slow progression to pulmonary metastasis (median 36 months),[1,7,16] once lung nodules are detected further metastatic work up is seldom performed.[3,16] Patients may in rare cases present with metastatic disease of unknown origin, case in point our patient with positive right pleural effusion and positive 4R lymph node. To our knowledge this case represents the second report with exfoliated metastatic adenoid cystic carcinoma in pleural fluid, the first being a case report by Florentine et al.[2] Despite the relatively common pulmonary and pleural involvement of advanced metastatic ACC, exfoliation of this tumor type into pleural fluid appears to be a rare event.[2,12] The general incidence of regional or distant lymph node metastasis in ACC is rare.[1,8,11,15,21,22] Primary site and lymphovascular invasion are significantly associated with lymph node metastasis.[21] In a study of 42 patients by Ko et al,[11] regional lymph node metastasis and tumor size (≥ 3cm) had a significant effect on distant metastasis. Similar findings were reported by Spiro et al[16] in their study of 196 ACC patients. However patients with no discoverable primary tumor, as seen in our patient, have not been described in larger series.

Adenoid Cystic carcinomas especially of the minor salivary glands should be treated with radical excision and post operative radiotherapy for the best chance of long term survival.[6,8,10] Short term prognosis is good but long term prognosis is poor, especially for ACC arising in minor salivary glands, with reported survival rates at 5 years 71-89%, at 10 years 29-71%, and at 15 years 29-55%.[3,4,6,11] It is generally accepted that positive surgical margins, nerve involvement and lymphovascular invasion may be associated with local failure or distant metastasis in patients treated for ACC.[10,14] Adjunctive radiotherapy is especially beneficial for patients with positive resection margins and solid growth pattern, in those with advanced operated tumor and in those with distant metastasis.[3] Only patients with lymph node metastasis may benefit from lymphadenectomy.[5,14,22] The complete surgical removal of all metastatic lesions in the lung has been reported in some studies to confer long term survival and potentially cure.[17] Radiation therapy used alone has a high rate of local recurrence but may provide useful palliation in inoperable / disseminated disease.[1] The use of concurrent chemotherapy has been reported sparingly,[23] and where used has not conclusively proven to be very effective.[12]

CONCLUSION

Salivary gland-type lung cancers are a group of low-aggressive entities with a higher tendency to recurrence/metastasis. Pathologists / cytologists need to be cognizant of the various body sites where adenoid cystic carcinoma can occur and include it in their differential work up.[2] Complete surgical resection with or without post-operative radiotherapy or radiotherapy alone in non-resectable cases is the current treatment of choice.[14] Long latent periods for some tumors suggests that 5 year follow up could be too short and patients need regular control for 10 years.[10]

CONFLICT OF INTEREST

The author has no conflict of interest to disclose.

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