Primary Cutaneous Adenoid Cystic Carcinoma with Pulmonary Metastases, Five Years after the Initial Diagnosis: Case Report and Literature Review

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Abstract

Adenoid cystic carcinoma is a malignant neoplasm mostly originating from the salivary glands but it has also been reported to arise in several other sites including the skin. Primary cutaneous adenoid cystic carcinoma (PCACC) was first described by Raul Boggio in 1975. Case reports then followed describing similar tumors with some reporting a metastatic tumor at presentation, and others reporting late metastases occurring as late as 21 years after initial diagnosis.

We report a case of a 65 year old male patient who presented with pulmonary metastases from a scalp adenoid cystic carcinoma diagnosed 5 years previously. A brief literature review is included which focuses on discussion of the behavior and prognosis of these lesions and their potential to metastasize. Metastasis of this tumor is more ominous than originally suggested; as the metastatic rate is close to 10% and can appear after a long time span which mandates a long term follow up.

We also challenge the reliance on thyroid transcription factor (TTF1) immuno-histochemical stain to differentiate primary pulmonary from metastatic adenoid cystic carcinoma. Our case and the experience of other researchers reveal that TTF1 can be positive in pulmonary metastases but negative in the primary lesion.

Keywords: Primary cutaneous adenoid cystic carcinoma, Lung metastasis, Thyroid transcription factor.

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Introduction

Adenoid cystic carcinoma (ACC) is a rare tumor which arises in many sites, but is best known as a primary salivary gland neoplasm. Its occurrence as a primary skin tumor is rare and our knowledge about its behavior depends mainly on case repots, the first of which was reported by Boggio's letter in 1975[1]. It is generally thought that primary cutaneous adenoid cystic carcinoma (PCACC) is an indolent tumor although case reports describe distant metastases especially to the lungs and the lymph nodes[2-5].

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We report a case of PCACC arising in the scalp which metastasized to the lungs five year after initial diagnosis. The metastasis in this case is extensive as it manifested with multiple, bilateral lung nodules.

Reviewing the literature revealed approximately 10% metastatic rate, which we believe is worse than the usually quoted statement that these lesions have a low metastatic potential.

Our case also posed a problem regarding TTF1 stain. The skin lesion was TTF1 negative whereas the metastatic one showed focal nuclear positivity. This could raise a doubt about the origin of the patient's neoplasm, as TTF1 is usually positive in primary lung tumors. However, the five year span between the two lesions, the multiplicity of the lung nodules, as well as the clear chest CT scan at the time of the initial diagnosis, all support that the primary lesion is of skin origin. Other researchers found similar findings regarding the TTF1 positivity in ACC arising in extra-pulmonary sites.

Case Report:

The first presentation of our patient was to the dermatology clinic in 2010 with a scalp mass of a long term duration which was firm , painless and attached to the underlying subcutaneous tissue. He was 60 years old at the time and of good general health.

The mass measured 15 x 15 x 5 mm and was removed under local anesthesia with the clinical impression of a sebaceous cyst. Histological examination showed an infiltrative tumor that was diagnosed as a malignant sweat gland tumor at the time.

A chest X ray as well as brain and neck computerized tomography (CT) scans were performed which ruled out metastatic lesions. The parotid and submandibular glands were also normal at the time apart from tiny calcifications in the lower pole of the left parotid gland.

As the tumor was incompletely excised from both deep and lateral margins, a re-excision was done but failing to free the deep surgical excision margin. No further action was taken and no other treatment was offered to the patient.

Five years later, the patient presented with shortness of breath on exertion. Chest X-ray was performed revealing a right sided pleural effusion with underlying passive pulmonary collapse.

Chest CT scan revealed pleural thickening and multiple bilateral large pulmonary nodules suggestive of metastatic lesions. The largest nodule was on the lateral segment of the right lower lobe and was 35mm in maximum dimension. Moreover pericardial and subcarinal lymph nodes were seen, the largest measuring 24 mm in short axis.

CT scan showed enlarged right posterior triangle and right occipital lymph nodes, the largest measuring 10mm in short axis. The parotid, submandibular glands and paranasal sinuses were normal. Brain and abdominal CT scans were unremarkable.

CT guided lung biopsies were obtained from the largest lung nodule described above using 18G needle, a procedure that the patient was reported to tolerate well.

The sections taken from these biopsies showed cores of lung tissue infiltrated by a tumor composed of bland looking basaloid cells in nests and columns concentrically arranged around pseudo-glandular lumina filled with

Periodic acid–Schiff (PAS) positive basement membrane material. True glandular lumina were also identified (Figure 1). The tumor cells lining the true glandular lumina were immunoreactive for c-kit (Figure 2), focally for carcinoembryonic antigen (CEA) while those around pseudoglandular spaces stained positive for S100 immunohistochemical stain. These histopathological appearances as well as the immunostaining pattern described above are typical of adenoid cystic carcinoma (ACC).

Considering the patient's history, and in order to investigate if this ACC is a primary lung lesion or a metastatic lesion from the previous skin tumor, we reviewed the archived Hematoxylin and Eosin stained sections of the previous scalp tumor. The skin lesion was morphologically similar (Figure 3), so we performed the above mentioned immunohistochemical stains on the skin tumor and it showed identical staining pattern to that seen in the lung biopsy (Figure 4).

Given the similar histological and immunostaining features as well as the radiological findings of multiple lung masses and the five -year span between the appearance of both tumors, we concluded that the lung ACC is metastatic from the primary cutaneous adenoid cystic carcinoma (PCACC) of the scalp. The initial scans in 2010 excluded any other primary as the parotid, submandibular and paranasal sinuses were normal at that time as compared with the subsequent scan five years later.

The pulmonary ACC of our patient exhibited focal positivity for thyroid stimulating factor (TTF 1) (Fig. 5) whereas his skin ACC was negative with this stain (Figure 6). This finding has perplexed us because TTF1 is thought to be specific for lung and thyroid tissue. Histopathologists rely on this stain to differentiate primary pulmonary neoplasms which are usually positive for TTF1 from metastatic tumors that are negative. Our case shows the reverse which was puzzling till we found similar results obtained by other researchers, a brief discussion of their results is included in discussion below.

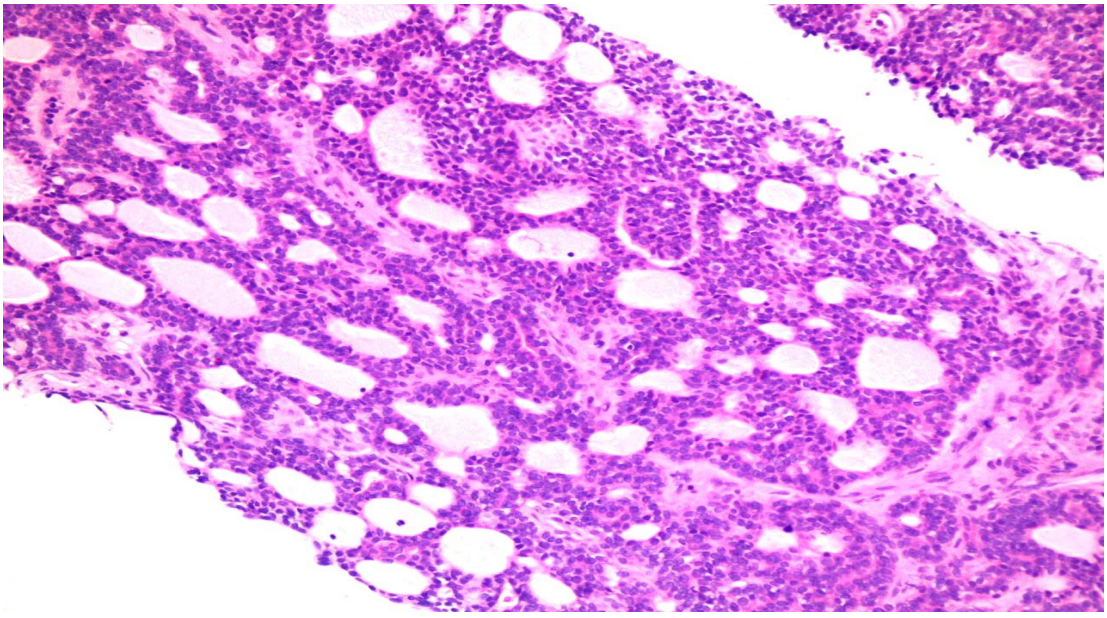

Figure 1: Metastatic adenoid cystic carcinoma to the lung; H & E stain, showing cribriform pattern of growth

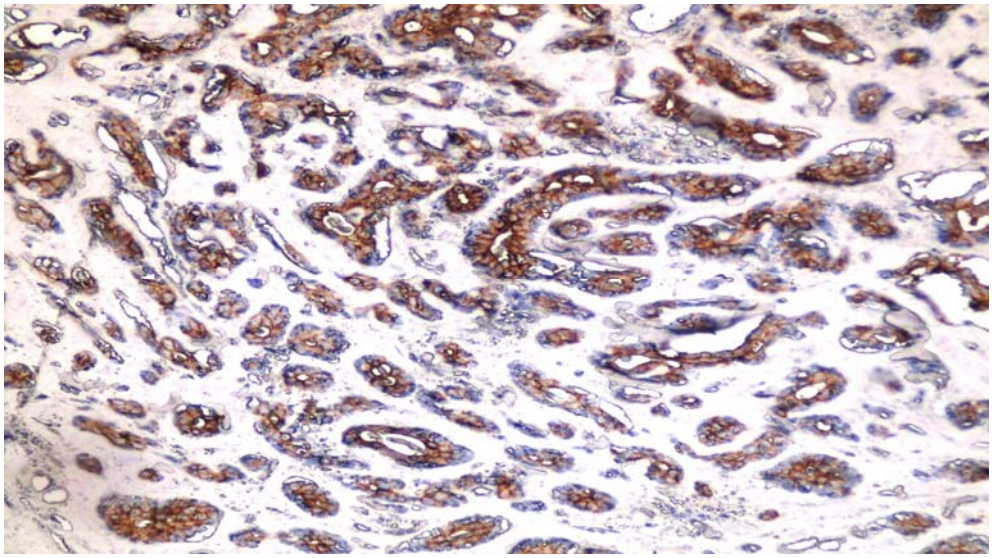

Figure 2: Positive c-kit stain in the metastatic ACC

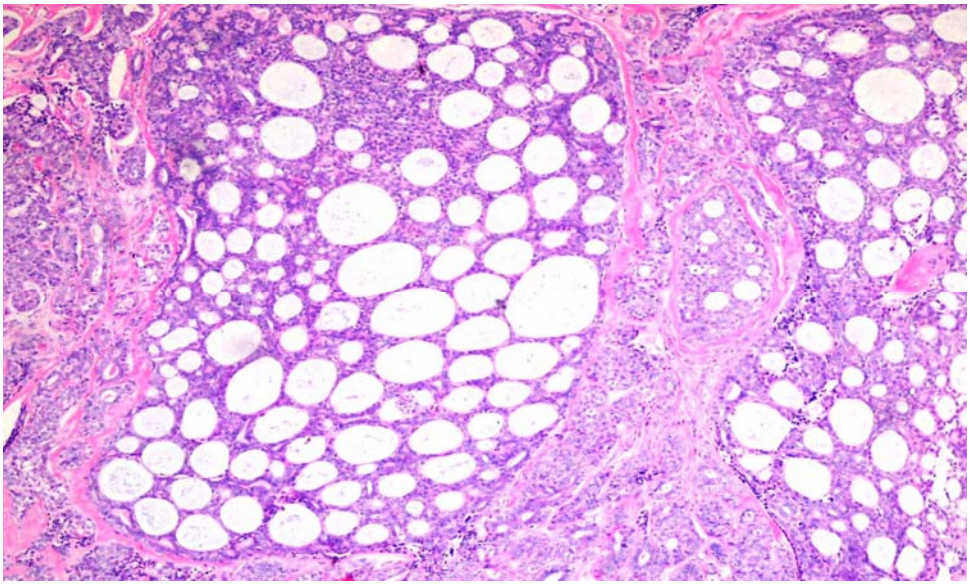

Figure 3: Skin lesion removed five years prior to the pulmonary metastasis, H & E stain

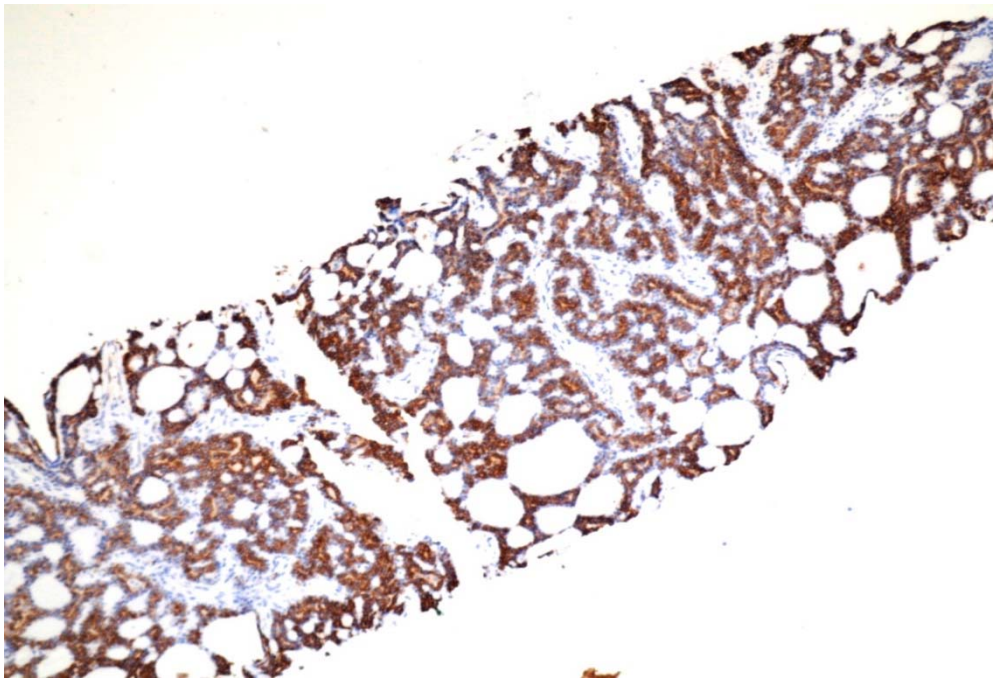

Figure 4: Positive c-kit stain in the PCACC

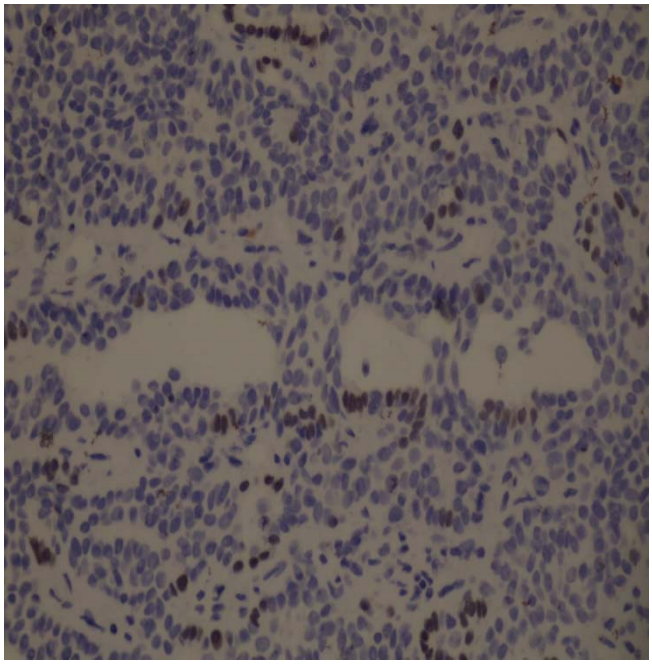

Figure 5: TTF1 stain in the pulmonary ACC showing focal nuclear positivity

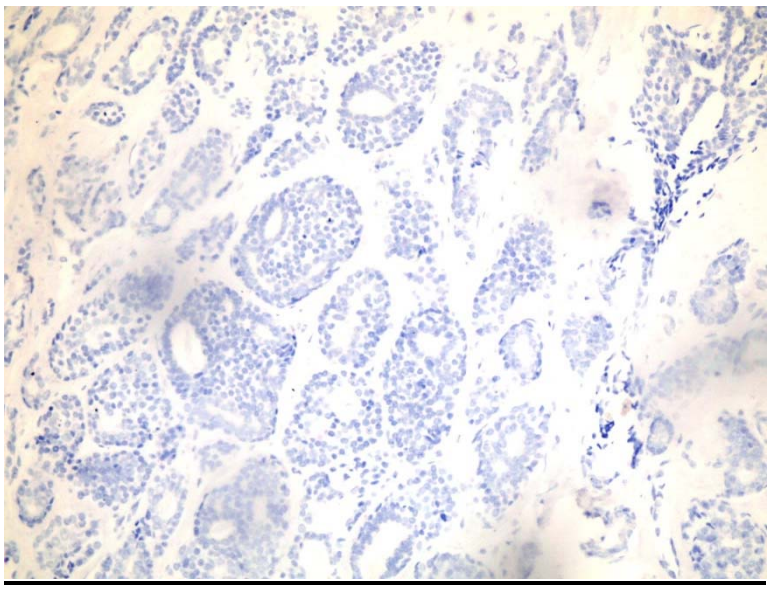

Figure 6: TTF1 stain in the PCACC which is completely negative

Discussion

Although adenoid cystic carcinoma is best known as a salivary gland neoplasm, it can arise in several other sites including the skin. The current knowledge of primary cutaneous adenoid cystic carcinoma is limited and mainly dependent on case reports and relatively small series of cases.

WHO classifies this tumor as a skin adnexal tumor, the origin of which is uncertain. It was originally thought that PCACC arises from eccrine sweat glands. However, the current view is that it arises from apocrine glands[5-7]. A piece of evidence supporting this claim is that adenoid cystic carcinoma of the external auditory canal arises from ceruminous glands, which are modified apocrine sweat glands[6, 7].

There are several reported cases of PCACC along with occasional series of cases, the largest, and most recent studied 152 cases diagnosed in the USA[8]. This study concluded that PCACC is a rare entity which affects men and women equally and it occurs predominantly in the head and neck region. Like all other publications, this one emphasized the importance of excluding other primary sites before diagnosing a primary cutaneous adenoid cystic carcinoma.

The behavior of PCACC is reported to be indolent with most references quoting a 50% recurrence rate and a rare risk of metastasis.[9,10,16]

The small number of reported cases makes it difficult to be certain about the true metastatic rate. In Doris et al series mentioned above[8]; 5% of cases with specified stage showed metastatic disease at the time of presentation. No details in this review are available about these cases and as the study mentions, there was no histological review of the cases. This raises a question about the validity of this figure (5% metastatic rate). It is also difficult to justify how these cases were diagnosed as primary skin tumors if several sites were involved at the time of diagnosis; this contradicts the recommendation in this and other studies

regarding diagnosing PCACC only if other primary sites are fully investigated.

In other series[9], it was fund that 5/50 (10%) of the reported cases showed visceral metastases. Another series of 49 cases revealed 12% rate of distant metastases (6/49 cases)[10]. A close figure is found in a review of 37 cases[11] where 3 cases showed lung metastases and 2 with lymph node metastases (13.5%) whereas Pappo et el found 3/25 cases having pulmonary metastases (12%)[4].

The value of these rates is restricted by the small number and by the fact that in some studies the length of follow up is not stated. With this in mind, we still think these rates reflect an incidence that is higher than the usually quoted statement that PCACC rarely metastasizes. In our opinion a number close to 10% is not an insignificant figure when talking about the risk of metastatic disease and this warrants a more radical treatment than just a wide local excision.

The case we report here is another example of the importance of a wide excision with adequate safety margins along with consideration of adjuvant radiotherapy or even chemotherapy. The initial excision in our patient was not adequate and further excision failed to clear the deep margin, this possibly contributed to the metastatic risk.

Our case also demonstrates the need for long term follow up in patients with PCACC. The metastasis in this case occurred 5 years following the initial excision.

Our case also highlights that TTF-1 immunohistochemical stain can be positive in tumors metastasizing to the lung. This poses a problem to histopathologists who usually consider TTF-1 a specific marker that can be relied on to differentiate primary from secondary lung neoplasms. The TTF- 1 staining in our case was positive in the metastatic lesion but not the primary one. This pattern mirrors the experience of Jungsuk et al in their recent study of 40 extra-pulmonary adenoid cystic carcinomas from various sites[12], two of these were PCACC. All these primary tumors were negative with TTF1. Ten of the forty cases metastasized to the lungs, of these 5 (50%) exhibited TTF1 positivity; however none of the metastatic cases were of cutaneous origin.

On the other hand, a case series of 21 cases of primary adenoid cystic carcinoma of the tracheobronchial tree showed that none of the tumors were positive for TTF-1 immunohistochemical stain[13]. This suggests that primary pulmonary ACC is usually negative with TTF1 but the small sample number makes it difficult to be conclusive about this issue. More work needs to be done to establish if this result can be generalized.

In conclusion, we report a case of PCAA carcinoma with pulmonary metastases five years after excision. Literature review reveals that PCACC is a rare skin adnexal tumor, which carries a significant risk of local recurrence and possibly a higher than previously thought risk of metastatic spread. This shows the importance of adequate excision with consideration of adjuvant therapy. Long term follow up is mandatory.

More work needs to be done to try to find factors that increase the risk of distant spread in order to select patients who need further treatment. Also, clinical studies to test the efficacy of adjuvant therapy in controlling local recurrence and decreasing risk of metastasis need to be performed.

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السرطان الغدي الكيسي الجلدي المنتشر إلى الرئة بعد خمس سنوات من التشخيص الأولي: تقرير حالة ومراجعة الأدب

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الملخص

السرطان الكيسي الوعائي هو ورم خبيث يصيب غالبا الغدد اللعابية لكنه قد يصيب انسجة اخرى بما فيها الجلد. أول من وصف السرطان الكيسي الغدي الاولي في الجلد هو رول بوغيو عام ١٩٧٥ ثم تتابع نشر التقارير المماثلة. بعض التقارير وصف انتشارا للمرض وقت التشخيص وبعضها وصف انتشاراً متأخراً بعد سنوات من التشخيص الأولي وصلت لواحد وعشرين عاما في إحدى الحالات

نحن نصف هنا حالة لمريض يبلغ من العمر ٦٥ عاما شُخّص بسرطان كيسي غدي أولي في جلد فروة الرأس ثم انتشر هذا السرطان إلى الرئة بعد خمس سنوات. قمنا أيضا بمراجعة وجيزة للحالات المماثلة المنشورة وناقشنا احتمالية انتشار هذه السرطانات التي نعتقد أنها تتسم بسلوك أسوأ مما يُعتقد مما يُحتم متابعة المرضى لفترة أطول.

للتفريق بين السرطان الكيسي الغدي الأولي والثانوي TTF1 نحن أيضا نتحدى فكرة الاعتماد على صبغة في الرئة ونُدعّم هذا بتجارب مشابهة منشورة.

الكلمات الدالة: التشخيص الأولي، السرطان الغدّي الكيسي الجلدي، الرئة.