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Case Report

Primary Cutaneous Adenoid Cystic Carcinoma of the Lower Limb: Rare Tumor in a Rare Location. A Case Report and Brief Review of Literature

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Abstract

Adenoid Cystic Carcinoma (ACC) is a rare entity with a predilection site at the salivary glands. Cutaneous localization is rather exceptional. Despite its rarity, it has a very distinctive histology consisting of cribriform epithelial structures which form pseudoglandular spaces giving a characteristic 'swiss cheese' appearance. Those pseudoglandular areas contain basement membrane-like material. The tumor has also the tendency for perineural invasion, that is responsible for its aggressiveness. We describe a case of a 60-year old male presenting with a pretibial asymptomatic pigmented dermal nodule on the lower leg. Histological examination was consistent with the characteristics of an ACC. After thorough examination we excluded localization elsewhere in the body and confirmed the primary cutaneous origin. In this case report we also briefly refer to the histogenesis, the morphological and molecular profile, the differential diagnosis, the therapeutic options and the management of the Primary Cutaneous Adenoid Cystic Carcinomas (PCACCs).

Keywords: Primary cutaneous adenoid cystic carcinoma; Skin cancer; Tibia

Introduction

Adenoid Cystic Carcinoma (ACC) is a malignant tumor that accounts for 22% of all salivary gland malignancies [1]. ACC of primary cutaneous origin is very unusual and was first described in 1975 [2]. Up to date, less than 70 confirmed cases of Primary Cutaneous Adenoid Cystic Carcinoma (PCACC) have been reported in the English literature. Many characteristics of this type of ACC, including its histogenesis, have not been fully discovered. It is hypothesized to be originated from apocrine origin [2,3]. There is a slight predilection for females and middle-aged individuals [4]. PCACCs are mainly located at the upper part of the body. The scalp is the most commonly affected region in over 40% of the cases, where it can lead to focal alopecia [2,5]. Combined with the neck and face, it accounts for 68% of all PCACCs. The chest region is affected in 19% of the cases [2]. Presence at the rest of the body, like the vestibular glands or lower limbs, is very seldom reported.

Most PCACCs are asymptomatic. Symptoms of pruritus, tenderness and alopecia have been described, especially when located at the scalp. PCACCs grow slowly and tend to be locally aggressive, with a high local recurrence rate seen in over a third of all cases [4,6,7]. Perineural invasion is an important risk factor for local recurrence, as the relative risk doubles from 22% to 44% in its presence [5]. Metastases are mostly seen after many years and occur in nearly one in six patients. A third of those is found in lymph nodes, whereas, the other two third is seen in viscera, mainly the lungs and the brain [8]. The treatment of PCACC is based on expert consensus, being a wide excision of the tumor with a two centimeters margin, to minimalize the risk of local recurrence [8].

The use of additional radiotherapy in case of perineural invasion is controversial [5,7]. Lifelong follow-up consisting of imaging and dermatological review to check for recurrence or metastasis is advised, due to the lifelong risk of metastases [4,7].

Histologically, PCACCs show a cribriform, tubular or solid architecture [4]. Pseudoglandular spaces, are responsible for the 'swiss cheese' appearance. Those pseudoglandular areas contain basement membrane-like material, which is positive for collage type IV and Periodic Acid-Schiff (PAS) stain [9]. PCACCs invade the dermis and might extend into the subcutis [10]. Immunohistochemically the epithelial cells lining the lumen are known to be positive for CD117, CEA, CK7 and sometimes BerEp4, while the myoepithelial cells, surrounding the cell islands, are p63 and SMA positive. The presence of those two different cell populations is important in making the histological diagnosis [6].

Case Report

We report a case of a 60-year old male presenting with an asymptomatic pigmented subcutaneous nodular lesion on the right tibia, showing a slow growth and rather indolent behavior. The lesion was approximately 1.5 by 0.5 centimeters. Clinical and family history were negative. Besides the pretibial nodule, physical examination was normal. The lesion was resected for further histological examination. Histological examination showed a nodular lesion reaching into the subcutaneous tissue (Figure 1), composed of small, monomorphic basaloid cells with small, round to oval nuclei and scant cytoplasm. A cribriform pattern with variably sized pseudoglandular spaces forming a "Swiss cheese"-like pattern is mainly seen, with focal accumulation of basement-membrane-like material (Figure 2). However, there are also a few solid areas (overall less than 30 %). There is evident mitotic activity. The surrounding stroma shows a desmoplastic response.

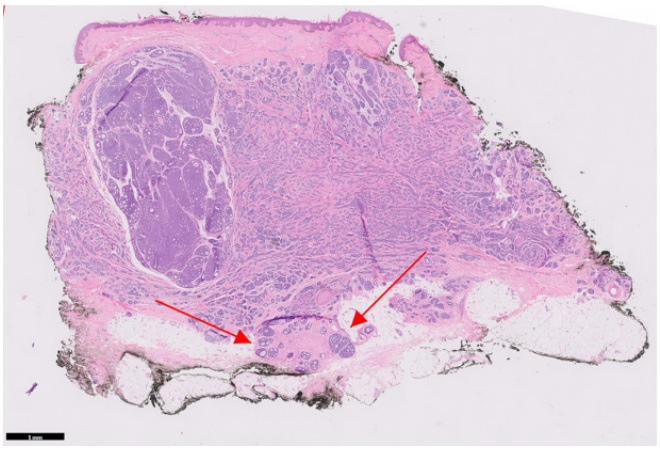

Figure 1: HE x10: panoramic view of the tumor, there is extension to the subcutaneous fat tissue (red arrows).

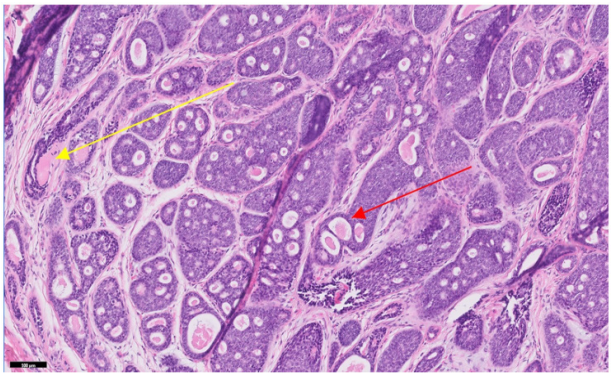

Figure 2: HE x100: pseudoglandular spaces forming a "Swiss cheese"-like pattern (red arrow) and accumulation of basement-membrane-like material (yellow arrow).

We also see perineural invasion, which was confirmed by the S100 immunohistochemical staining (Figure 3 and 4). Immunohistochemical examination revealed CD117 positivity of all tumor cells (Figure 5). In the additional PAS histochemical staining we found PAS positive material in the lumen of the pseudoglandular structures (Figure 6). Next generation sequencing, using the Oncomine Focus Assay with QIAamp DNA Mini Kit, did not show any significant mutations, among which no BRAF and NRAS gene mutations. Furthermore, fusions at RNA level were investigated, with no findings. The generalized positivity for CD117 combined with the morphology and the perineural invasion confirms the diagnosis of an ACC. Microscopically, the tumor was incompletely excised.

As an ACC is a malignant entity, further staging needed to be done. Full body skin examination and a thorough radiological examination, consisting of a Computer Tomography (CT) of the thorax and abdomen combined with ultrasound of the lymph nodes, was performed to check for other tumor localizations.

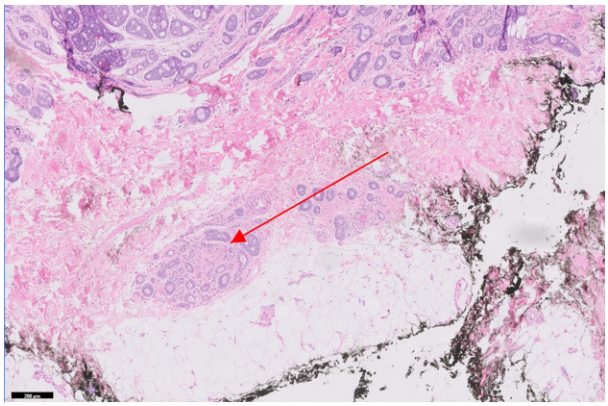

Figure 3: HE x50: perineural invasion (red arrow). The nerve is surrounded by neoplastic cells.

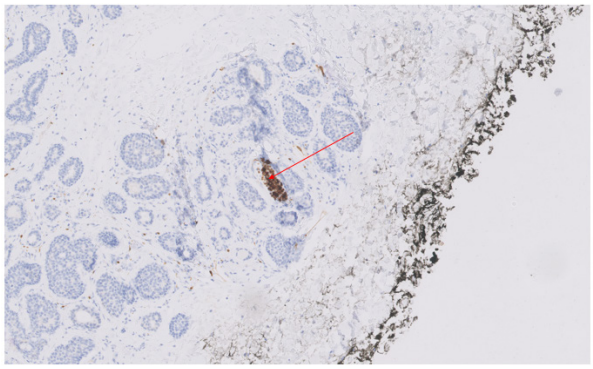

Figure 4: S100 (DAB) x50: perineural invasion. The nerve is staining positive for S100 (red arrow). The nerve is surrounded by neoplastic cells.

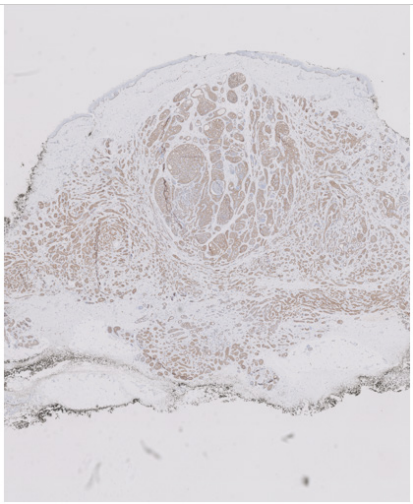

Figure 5: CD117 (DAB) x10: positivity in almost all neoplastic cells.

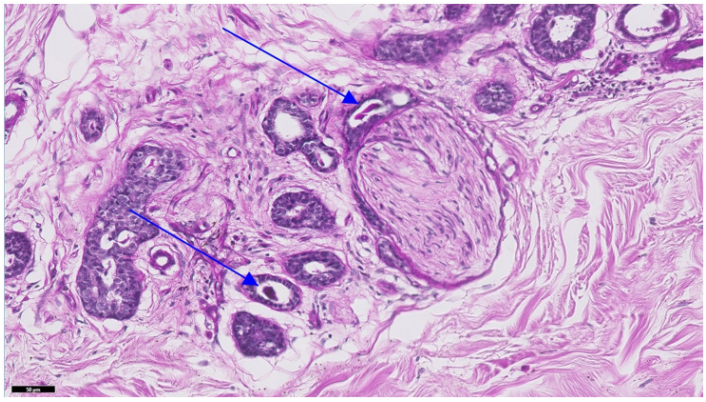

Figure 6: PAS staining x200: PAS positive material in the pseudoglandular spaces.

Those revealed no other suspicious lesions, confirming the primary cutaneous origin without distant metastases, compatible with a PCACC. Considering an incomplete previous resection without any distant metastasis, a wide local excision was performed. The margins were free of tumor cells, but not conform the expert consensus of a two centimeters wide resection margin. Therefore, a third excision was performed, leaving a wound of 13 by 3 centimeters, which was reconstructed using a split thickness graft, with the left thigh as donor site. Lifelong follow-up was advised in the form of annual full body skin examination, low dose CT of the thorax and abdomen, and ultrasound of the inguinal lymph nodes, to check for local recurrence or metastases. The patient is doing well with no local recurrence or metastases after a year of follow-up.

Discussion

ACC is a tumor that is frequently seen in salivary glands. However, primary cutaneous presentation is rare and mainly located at the upper part of the body [2]. Other locations have been described. However, presentation at other locations is extremely rare. PCACCs are slow growing but progressive. PCACCs are mostly asymptomatic, but can cause pruritus or alopecia if located at the scalp [4,5] Presence of perineural invasion is important, as it nearly doubles the risk of local recurrence [5]. The important differential diagnoses of PCACCs are Basal Cell Carcinoma (BCC), cylindroma and metastases of ACC elsewhere in the body. The distinction with a BCC of adenoid variant is based on immunohistochemistry for CD117. Instead of focal positivity in case of BCCs for the adenoid-type cells, a PCACC shows diffuse positivity for CD117, namely in all tumor cells [11].

Furthermore, perineural invasion and extension in to the subcutis characterizes the malignant features of a PCACC, differentiating it from the benign tumors like cylindromas [12]. The distinction with a metastasis of an ACC elsewhere in the body is made based on the imaging and dermatological examination searching for other tumor sites [8]. If those are negative, an metastases of an ACC can be excluded and the diagnoses of a PCACC can be made. Additional Ultrasound (US) for reviewing the salivary glands was not done in this particular case. Moreover, this was not done because CT is recommended over ultrasound as imaging modality for detecting lesions in the salivary glands [13]. Another research groups states that there is no superior image modality, so US an CT would perform equally [14]. Therefore, as the patient already did undergo a CT, there was no need for an US of the salivary glands.

The exact histopathogenesis of PCACCs is not fully known. It is debated whether it arises from apocrine or eccrine sweat glands, though an apocrine origin is favored [2]. A mutation in the

MYB-gen is described in 40% of the PCACCs. This is an proto-oncogene that accounts for hematopoiese, neuronal development and homeostasis of the colonic crypts [7]. It is hypothesized to play a role in the etiology. The tumor in this case report was not tested for MYB-gene mutations. On histological ground, Alkan et al. argue that the identification of two different cell types is essential [6]. The epithelial cell line would be positive for CD117, CEA CK7 and might be positive for BerEp4, while the myoepithelial cells show positivity for p63 and SMA [6]. However, Rocas et al. state that PCACCs are positive for keratins, EMA, S-100 protein and CEA, but argue that p63 positivity is not obligatory [2].

In our case the tumor is positive for CD117, while S-100 is negative in the tumor cells but positive in the nerves, confirming the perineural invasion. The treatment is based on expert consensus, consisting of a wide excision with a margin of 2 centimeters, combined with annual follow-up, in the form of imaging and dermatological review, to check for local recurrence and late metastasis [8]. The use of adjuvant radiotherapy is debated as it might decrease the chance of local recurrence in case of locally aggressive disease with perineural invasion, or could be used when complete excision is doubted [5,15]. Nevertheless, it causes scarring of the surrounding healthy tissue [4]. Only a few cases of distant metastases have been described in literature. Two patients showed regression of tumor size after chemotherapy. Singh et al, described a substantial regression of the primary tumor after two cycles of cisplatin combined with 5-fluorouracil in a patient that refused surgery. Moreover, the patient was still alive after 15 months [15]. Another patient with multiple metastases was treated with adjuvant chemotherapy, consisting of 2 cycli of cisplatin combined with adriamycine, and showed complete regression of those metastasis [16]. Therefore, chemotherapy seems a good therapeutic modality in case of distant metastasis.

Numbers on overall survival after diagnosis of a PCACC are scarce. Dores et al. estimated the 5 year overall survival to be 96.1%. However, tumor localization at the face, head or neck, had a better overall survival than PCACCs at the chest region, with percentages of 99.1% and 75.6% respectively. Moreover, females had a slightly worse overall survival of 88.6%, compared to men with a 98.5% overall survival after 5 years. In their study, only 16 patients had a PCACC localized at their extremities, and only 4 patients had distant metastases at the time of diagnosis. Therefore, the overall survival for these specific groups could not be estimated by Dores et al [4]. In general, these numbers show a good prognosis for a PCACC.

In conclusion, we present an rare localization of a PCACC. The histology of cribriform structures with the typical 'Swiss-cheese' morphology, together with the infiltrating growth pattern, the perineural invasion and the positivity of the cells for CD117, confirms the diagnosis of an ACC. Given its rarity, PCACC is an exclusion diagnosis based on the lack of other tumor sites besides the skin. Lifelong follow-up is important as the tumor can recur or metastasize even after many years. In our case, no local recurrence or distant metastasis were seen a year after initial diagnosis.

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Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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