

Case Report

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# Cutaneous Adnexal Carcinoma with Apocrine Differentiation: A Challenging Diagnosis and Personalized Treatment with mTOR Inhibitor in a Very Rare Disease

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## Keywords

Cutaneous adnexal carcinoma · Next-generation sequencing test · PI3KCA mutation · Everolimus

## Abstract

Cutaneous adnexal carcinoma with apocrine differentiation is a rare neoplasm arising from cutaneous adnexa, especially of the head and neck and trunk region. Because of its rarity, the diagnosis is challenging and often impossible to distinguish from metastatic cutaneous adenocarcinoma of the breast. The standard of care remains surgery for resectable disease. To date, univocal guidelines for metastatic disease are lacking, particularly regarding systemic therapy. We report a clinical case of a patient diagnosed with cutaneous adnexal adenocarcinoma with apocrine differentiation of the left axilla with lymph node and bone metastasis. We started with carboplatin and paclitaxel chemotherapy regimen, with good response. After progression, we performed a next-generation sequencing analysis (by the Foundation One CDx test) to identify genomic alteration in cancer-related genes. We found PIK3CA and KRAS mutations. Due to this result, the patient started a second-line treatment with a personalized therapy including an mTOR inhibitor, everolimus, and, to date, he is still under treatment. To our knowledge, this is the first case of a patient responding both to chemotherapy and to a personalized treatment with an mTOR inhibitor. It is important to support the value of genomic screening in this rare neoplasm.

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## Introduction

Cutaneous adnexal carcinoma with apocrine differentiation is a variant of rare neoplasms arising from epithelial adnexa usually included in a group of neoplasms called skin adnexal cancers (SAC) [1]. The primary sites of origin are often the head and neck or the trunk region, mostly in apocrine-dense areas. The prognosis is poor in advanced disease with a median survival of 14.5 months and a 5-year survival rate of 10% [2].

The differential diagnosis with cutaneous metastasis of breast cancer is often challenging, if not impossible in some cases because of overlap in tumor morphology [3]. Immunohistochemical markers may not be helpful to distinguish primary from metastatic lesions. However, the clinical history of the lesion may be very helpful to distinguish primary cutaneous cancer from metastases. In particular, a long-standing single lesion with a sudden growth in size is most suggestive of a primary cancer whereas multiple lesions located in the same anatomical region may indicate cutaneous metastases [4].

Because of the rarity of this cancer, there are no current uniform treatment guidelines. Surgery for the primary resectable tumor remains the standard of care. Radiotherapy can represent an option in case of unresectable disease or distant metastases. The role of chemotherapy in advanced disease is still unclear. There are only anecdotal cases treated with systemic chemotherapy or targeted therapies.

We report a single clinical case of a patient diagnosed with metastatic cutaneous adnexal carcinoma with apocrine differentiation responding to primary chemotherapy and targeted therapy after a next-generation sequencing (NGS) analysis for genomic profiling of cancer-related gene mutations (Foundation One CDx test) of the primary cancer.

## Case Report

A 61-year-old man presented, in May 2015, to our dermatological department with a 6-year history of a cutaneous, painful lesion of the left axillary region, progressively increasing in size. Physical examination revealed an erythematous, fibrotic and multilobular subcutaneous mass in the left axilla and local lymph node swelling. Cutaneous and nodal biopsies were performed leading to the diagnosis of adnexal adenocarcinoma with apocrine differentiation.

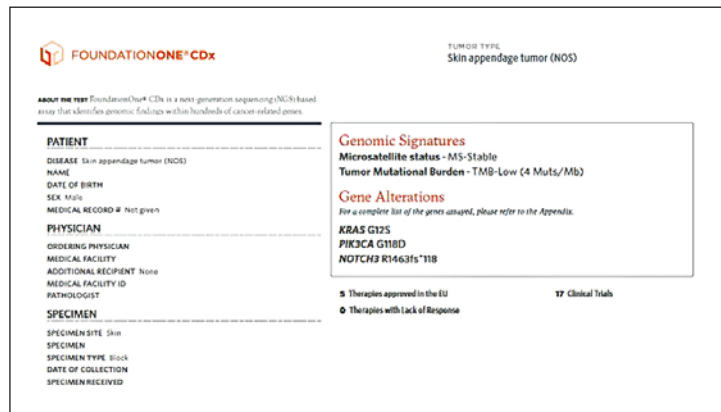
Furthermore, an  $^{18}\text{F}$ -FDG positron emission tomography (PET)/CT scan showed osteolytic bone lesions in the thoracic and sacral vertebrae, and mediastinal lymph node involvement. No other distant lesions were detected.

Because of pain and local diffusion, in July 2015, the patient underwent surgery of the primary cutaneous cancer and nodal regional dissection. The diagnosis of primary adnexal carcinoma with apocrine differentiation was confirmed. Immunohistochemical stains were positive for CK7 and EMA, negative for estrogen, progesterone, CK 20 and GCDFP15; HER2 was not amplified.

From October 2015 to February 2016, the patient received first-line chemotherapy with 6 courses of carboplatin and paclitaxel regimen obtaining a metabolic partial response. Palliative external beam radiotherapy on sacral vertebrae was also performed. He continued with the follow-up and zoledronic acid infusion every 4 weeks.

In October 2016, a new radiological evaluation with  $^{18}\text{F}$ -FDG PET/CT scan revealed a new site of radionuclide uptake in the retropectoral region as a single site of disease progression; therefore, the patient received external beam radiotherapy (40 Gy in total).

In September 2017, a new  $^{18}\text{F}$ -FDG PET/CT scan showed a progression of the bone/nodal disease with evidence of lung and soft tissue nodule appearance. Hence, because of a prolonged



**Fig. 1.** Gene alterations detected with the Foundation One CDx, a next-generation sequencing test.

time to progression, the patient received a chemotherapy re-challenge with carboplatin and paclitaxel for 6 courses obtaining a further partial response.

Left retropectoral nodes and soft tissue pectoral muscle nodules were detected in a follow-up <sup>18</sup>F-FDG PET/CT scan performed in February 2019. The performance status of the patient remained good.

Due to lack of evidence of the activity of other chemotherapy regimens, a next-generation sequencing-based assay (Foundation One CDx) was performed (Fig. 1) with the detection of 2 genes alternating that are potentially druggable, i.e., KRAS G12S and PIK3CA G118D. A third mutation of NOTCH3-R14&3 fs was detected, with no therapeutic or clinical trial options. Therefore, from March 2019, the patient has received anticancer therapy with an mTOR inhibitor, everolimus, 10 mg orally every day (Afinitor, kindly gifted by Novartis). The therapy has been administered together with a dexamethasone-based mouthwash to inhibit stomatitis, an everolimus-related side effect. After 3 months of therapy, the patient achieved a metabolic partial response (Fig. 2), and further <sup>18</sup>F-FDG PET/CT scans showed long-lasting stable disease with clinical benefit. The patient is still receiving everolimus therapy with good tolerability.

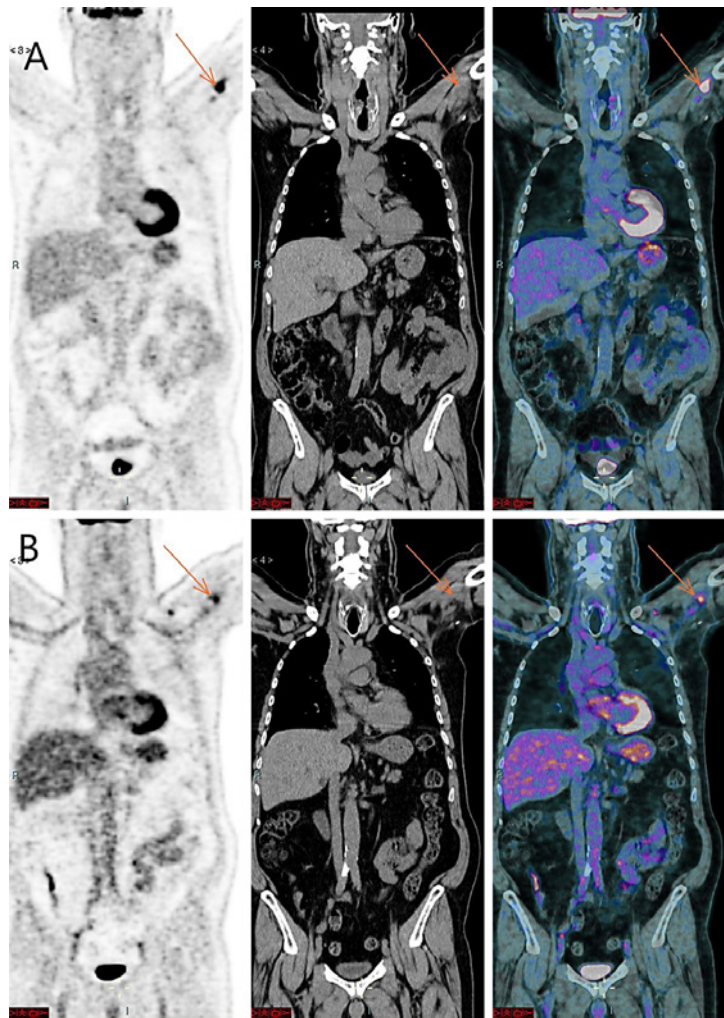
## Discussion

In the present case report, we describe a very rare disease presenting challenging aspects concerning both diagnosis and treatment. Histologically, the distinction between primary adnexal and metastatic breast adenocarcinomas can be very difficult and some authors argued that they are essentially indistinguishable [5].

Skin adnexal cancers are a group of rare cancers with poor prognosis and lack of therapeutic evidence. Because of their rarity, uniform guidelines are lacking, in particular for advanced disease. Many authors agree that the role of chemotherapy is unclear, although some cases have been reported to be responsive to single-agent or combined chemotherapy. Particularly a regimen including anthracycline, cyclophosphamide [6] or carboplatin and paclitaxel-based regimens were evaluated [7].

There are some cases of high-risk cancer treated with adjuvant radiotherapy [8]. However, radiotherapy has more often been employed for locally advanced disease or metastatic lesions.

Anecdotal clinical cases have been reported responding to some targeted therapies like sunitinib [9], and human epidermal growth factor receptor type 2 (HER2) inhibitors such as pertuzumab [10], lapatinib [11] and trastuzumab [12]. Furthermore, a response to immuno-



**Fig. 2.** Pre- (A) and post-chemotherapy (B)  $^{18}\text{F}$ -FDG PET/CT scans. PET, CT and fused PET/CT scans are shown in the left, middle and right panels, respectively. A reduction in the radionuclide uptake is evident in the main neoplastic lesion (red arrow) located between the left teres major and coracobrachial muscles (pre-therapy SUV and MTV 6.8 and 11.3; post-therapy 5.9 and 2.8). Both the dimensions and the glycolytic activity of the other 2 lesions around the larger one are basically unchanged.

therapy with pembrolizumab has recently been described in a case of metastatic microsatellite-stable sebaceous carcinoma [13].

As for our patient, in the absence of therapeutic options, we performed a next-generation sequencing-based genomic test (Foundation One CDx) to screen the presence of potentially targetable mutations. Indeed, we found 2 involving the PIK3CA and KRAS genes.

In a recent retrospective study, 45 cases of SAC were analyzed with a targeted next-generation sequencing test finding a gene mutation in 18 out of 45 cases. The most frequent mutations involved TP53 and PIK3CA (3 cases), supporting the importance of genetic analysis in patients with advanced SAC [14]. KRAS mutation was found in 1 patient in this study.

KRAS is normally involved in MAPK/MEK cascade and other effector pathways. Oncogenic KRAS mutations lead to hyperactive signaling that initiates and maintains tumorigenesis [15]. Preclinical and clinical evidence suggested that MEK inhibitor-based therapy, such as trametinib, could be useful in patients with KRAS mutated cancer [16].

PI3K is a cytoplasmic molecule downstream of KRAS and it is part of the PI3K/AKT/mTOR pathway. It is a site of convergence of multiple pathways and its regulation is complex. PI3KCA activation may predict sensitivity to mTOR inhibitors, including everolimus and temsirolimus.

Everolimus is well known to be active in kidney [17] and breast cancer in combination with aromatase inhibitor [18], but the mechanism of action including the PIK3CA/AKT/mTOR pathways is also involved in the development and progression of other neoplasms [19].

## Conclusion

To our knowledge, this is the first case reported of a patient diagnosed with SAC with a long-lasting response both to chemotherapy and targeted therapy. With the present clinical case, the authors emphasize the importance of knowledge of tumor gene mutations, especially in these rare cancers, in order to better “individualize” therapies. This suggestion is also supported by a retrospective study [14] where in almost all cases of analyzed skin adnexal cancer, it has been possible to detect a mutation. Further investigations are needed.

## Statement of Ethics

The patient in this case report has given written informed consent to the publication of the case details.

## Conflict of Interest Statement

The authors declare no conflicts of interest.

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## Author Contributions

Michela Libertini has dealt with the collection of literature data, with the selection of the case report and with the drafting of the article.

Ester Oneda has dealt with the drafting of the article.

Brunella Di Biasi has dealt with the acquisition of data.

Giordano Savelli has dealt with the revision of the article.

Alberto Zaniboni has dealt with the revision of the article and with the approval of the final version.

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