# Whole exome sequencing of a patient with metastatic hidradenocarcinoma and review of the literature

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## Abstract

Hidradenocarcinoma is a rare malignancy of the sweat glands with only a few cases reported in literature. The management of these tumors is based on the extent of disease with local disease managed with surgical resection. These can tumors carry a high potential of lymphatic and vascular spread and local and distant metastases are not uncommon. Given the rarity of the tumor and lack of genetic and clinical data about these tumors, there is no consensus on the proper management of metastatic disease. Here in we report the first case of metastatic hidradenocarcinoma with detailed molecular profiling including whole exome sequencing. We identified mutations in multiple genes including two that are potentially targetable: PTCH1 and TCF7L1. Further work is necessary to not only confirm the presence of these mutations but also to confirm the clinical significance.

## Introduction

Hidradenocarcinoma (HA) is a rare tumor of the sweat glands with an incidence as low as 0.05% in the general population.[1-4] In the Surveillance, Epidemiology, and End Results (SEER) data, the incidence rate of apocrine-eccrine carcinomas was 2.6 per 1 million person years from 1978 through 2005.[5] The face and the upper extremities are the most common sites of involvement but it can also involve the eyelid, scalp, finger and the perianal region.[6] While most of these tumors arise de novo, investigators have reported that these tumors can also develop from preexisting hidroadenomas.[7]

Based on histological classification, there are recognized variants including nodular hidradenocarcinoma, malignant acrospiroma, malignant clear cell hidradenomas and clear cell eccrine carcinoma. The natural course of the tumor includes local and frequently multiple recurrences.[8] As with all human cancers, there is variability in the clinical course of HA patients; however it is important to note that many will experience frequent local recurrences following their initial diagnosis and treatment. Not surprisingly, involvement of regional lymph nodes and the presence of distant metastases are associated with a poor prognosis.[9] Related to this, once metastatic disease is diagnosed 5 year survival drops to less than 50%.[5] Currently there are no uniform guidelines for the treatment of metastatic HA. Moreover, the molecular and genetic events that underlie these tumors are poorly understood. Motivated by this, we report the first case of metastatic HA with molecular profiling and identify possible targets for treatment on the basis of identified genetic mutations.

## Case Report

A 32-year old man with no significant past medical history presented with a several month history of a non-healing ulcerative lesion under his right axilla. On examination, multiple palpable subcutaneous nodules were present in the axilla, groin, face, neck and chest wall. Excisional biopsy of the axillary lesion showed a poorly differentiated HA (Figure 1). The diagnosis of carcinoma was supported by positive immunohistochemical staining for keratins (AE1/AE3 and CK7). In addition, the tumor was strongly positive for estrogen receptor (ER), but negative for Her/2neu overexpression. Staging with positron emission tomographic computed tomography (PET CT, Figure 2) scan showed multiple enlarged hyper-metabolic nodes in the right axilla and bilateral supraclavicular lymph nodes. A lytic lesion in the posterior right 5th rib was also seen. The patient was not thought to be a surgical candidate secondary to metastatic disease. A single case report in the literature found prolonged response to paclitaxel and carboplatin, and therefore, we offered our patient palliative cytotoxic chemotherapy with this regimen.[10] The patient completed three cycles of chemotherapy and restaging scans revealed progressive disease in the bilateral axilla. Given the progressive disease, chemotherapy was stopped and the patient received palliative radiation to his bilateral axilla, to which he had a significant response. Upon completion of radiation patient began tamoxifen, an estrogen receptor antagonist based on the ER positivity of his tumor and some success with tamoxifen in other ER positive hidradenocarcinomas.[11-13] At

13 months of starting tamoxifen, the patient remains without clinical progression.

In parallel to initiating treatment, an axillary lymph node was biopsied, the presence of metastatic tumor was confirmed, and the tumor tissue was sent for genomic profiling using Foundation One testing (Foundation Medicine, Cambridge MA, USA) as well as Baylor's whole exome sequencing (Baylor College of Medicine, Houston, TX, USA). The Foundation Medicine panel identified four genetic alterations including FGFR1 amplification, CDH1 splice mutation, MYST3 amplification and ZNF703 amplification (Table 1). The Baylor whole exome analysis identified no germline mutations, two cancer related and actionable genes, seven tumor associated genes, and approximately 180 variants in non-cancer associated genes (Table 1). The actionable cancer related genes identified in the Baylor panel included PTCH1 and TCF7L1, and the mutations in cancer genes without identifiable targets included ARID1A, CDH1, FBXO11, FNBP1, IL6ST, MYC, and WHSCIL1.

## Discussion

Hidradenocarcinomas are rare malignancies of the sweat glands, and due to the rarity, there is little evidence to guide therapeutic

options and even less information about the genetic and molecular alterations of these tumors. Herein, we report the first case of genomic analysis of this rare tumor and the potential actionable mutations.

Clinically, HA present as painless slow growing firm or cystic nodules. These tumors have high metastatic potential and frequently metastasize to the lungs, liver, and bone and usually have a very aggressive course. Immunophenotypically the tumors are positive for epithelial markers such as cytokeratin and CEA. Approximately 30% of apocrine-eccrine carcinomas tumors stain positive for ER by immunohistochemistry.[11-13] In at least one case, strong Her-2/neu positivity by IHC and gene amplification by fluorescence in situ hybridization (FISH) has been demonstrated.[14]

The standard of care for the treatment of localized HA usually includes wide local excision with clear margins. The role of a sentinel lymph node biopsy is unclear. In about 50% of moderately to poorly differentiated tumors, lymph node involvement has been reported.[15] While regional lymph node dissection is usually performed in clinically positive lymph nodes, the role of adjuvant chemotherapy and radiotherapy is not established.

The optimal treatment for patients with metastatic disease remains unclear. Multiple reports of chemotherapy have been published with variable efficacy and are summarized in Table 2 and outlined below.[16-27] A prolonged response for 16 months to carboplatin and paclitaxel was seen in a patient with metastatic apocrine carcinoma of the scalp; however the patient ultimately had scalp recurrence and brain invasion that led to his death.[10] A response to capecitabine up to 24 months was seen in patient with metastatic HA of the elbow.[16] A complete remission for 16 months was reported by Piedbois,[17] with combination chemotherapy including cisplatin, doxorubicin, mitomycin C and vincristine. Bellman *et al*.[18] reported a case of HA with metastases to the skin, which had excellent response to 5-fluorouracil. Mezger *et al.*[19] also reported two cases of metastatic HA treated with combination chemotherapy consisting of Adriamycin, cyclophosphamide, vincristine, and bleomycin with one of the two patients achieving a complete remission for two years before succumbing to brain metastasis and with the second patient achieving a partial remission lasting for only four months.[19] In another report use of cetuximab and cisplatin in a patient with axillary apocrine carcinoma with brain metastases had disease progression after two cycles.[20] Use of 5 FU and cisplatin resulted in disease progression within 6 months in another case.[21]

In addition to chemotherapy, targeted approaches have also been tried. Given that some tumors stain positive for ER, agents that inhibit the estrogen receptor such as tamox-
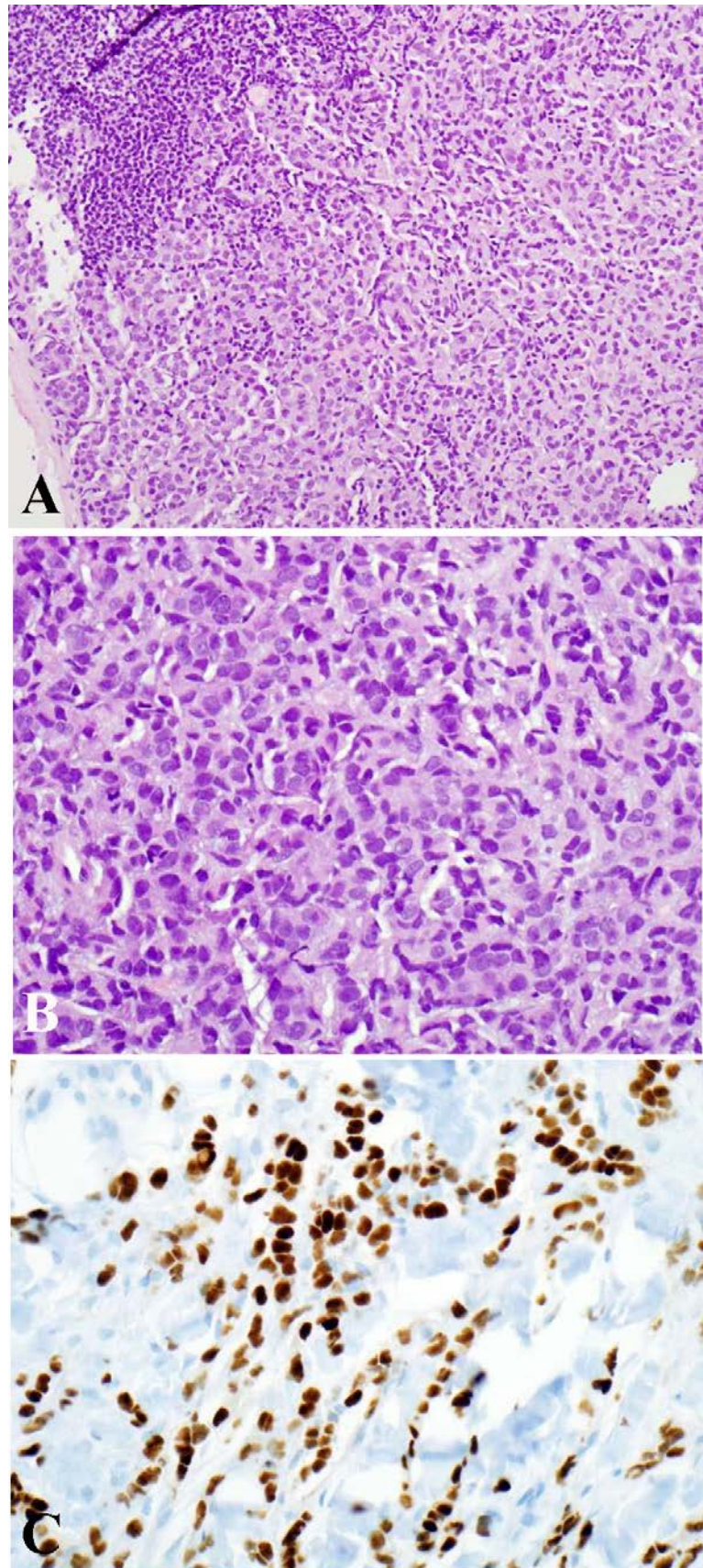


Figure 1. A) Lymph node with metastatic poorly differentiated adenocarcinoma. (H&E stain, ×200); B) higher magnification of the tumor showing a largely solid growth pattern. (H&E stain, ×400); C) immunohistochemistry for estrogen receptor, showing strong nuclear staining of the tumor cells (×400).

ifen have been explored with some success.[28] Sridhar *et al.* described a case report of ER positive eccrine adenocarcinoma of the scalp with lymph node metastasis.[13] The patient had excellent response to tamoxifen for three years but eventually had progressive disease to the brain, which was the terminal event. In an another case, tamoxifen induced disease free survival of three years in a patient with metastatic HA to the lymph nodes.[12] Given the benefit of anti-estrogen therapy, assessing the ER receptor and consideration of anti-estrogen therapy is reasonable. In addition to the lack of clinical data, there is also a large gap of molecular characterization of hidradenocarcinoma with a recent PubMed search for *hidradenocarcinoma* revealed only 75 references. A recent study utilizing a targeted sequencing of 15 cancer-related genes identi-
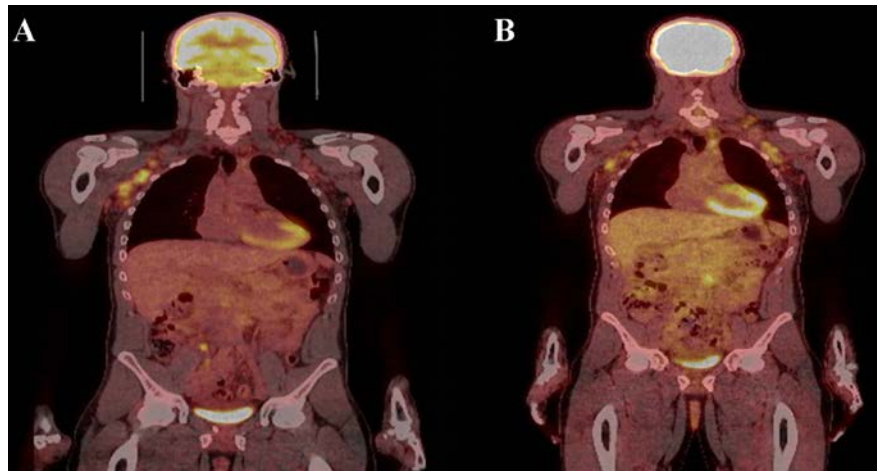


**Figure 2. Positron emission tomography showing disease (A) before and after (B) chemotherapy.**

**Table 1. Foundation Medicine Gene panel and Baylor whole exome sequencing.**

| Gene | Gene product name | Genomic event | Gene product | Potential impact of mutation |
|------|-------------------|---------------|--------------|------------------------------|
| FGFR1 | Fibroblast growth factor receptor 1 | Amplification | Tyrosine Kinase Receptor | Increased expression could allow for increased activation of MAPK pathway and cell growth. |
| CDH1 | E-cadherin | c.2439+1G>C | Cell adhesion | Loss of function mutations in CDH1 could allow cells to grow even in the presence of cell to cell contact |
| MYST3 | MYST histone acetyltransferase (monocytic leukemia) 3 | Amplification | Histone acetyl transferase | Increased expression could lead towards dysregulated epigenetic changes. |
| ZNF703 | Zinc Finger 703 | Amplification | Transcription Factor | Transcriptional corepressor which does notbind directly to DNA and may regulate transcription through recruitment of histone deacetylases to gene promoters |
| PTCH1 | c.C3641T | Missense | p.T1214M | Hedgehog signaling pathway |
| TCF7L1 | c.C710T | Missense | p.S237F | WNT/Hippo signaling pathways |
| ARID1A | c.G4468T | Nonsense | p.E1490X | Chromatin Remodeling |
| CDH1 | c.2439+1G>C | Splicing | p.E1490X | Cadherin C |
| FBX011 | c.G1993C | Missense | p.D665H | Ubiquitin protein ligase complex |
| FNBP1 | NM_025133 | Nonsense | cG1783T | Formin binding protein family |
| IL6ST | NM_002184 | Missense | c.T2532G | Jak-Stat pathway |
| MYC | NM_002467 | Missense | c.C459G | MYC amino terminal region |

**Table 2. Chemotherapy regimens used for metastatic hidradenocarcinoma.**

| Author | Primary tumor | Chemotherapy regimen | Duration of follow up |
|--------|---------------|----------------------|-----------------------|
| Tlemcani *et al.*[10] | Scalp | Paclitaxel + Carboplatin | Stable at 16 months |
| Lerner *et al.*[16] | Scalp | Capecitabine | Disease free at 24 months. |
| Piedbois *et al.*[17] | Labium majorum | Doxorubicin + Mitomycin + Vincristine + 5-FU | Complete response lasting for 16 months |
| Bellman *et al.*[18] | Eyelid | 5-Fluorouracil | Partial remission for 2 years |
| Mezger *et al.*[19] | Skin | Adriamycin + Cyclophosphamide + Vincristine + Bleomycin | Patient 1: complete remission lasting 2 years; Patient 2: |
| Gallerani *et al.*[20] | Axilla | Cisplatin + Cetuximab | Disease progressed after 2 months |
| Chintamani *et al.*[21] | Axilla and arm | Cisplatin + 5FU + Radiation | Disease progression within 6 months |
| Jouary *et al.*[22] | Elbow | Capecitabine | Stable at 18 months |
| Battistella *et al.*[23] | Skin, hair follicle | Sunitinib | Stable at 8 months; partial remission at 10 months |
| Kiyohara *et al.*[24] | Vulva | Cyclophosphamide + Anthracycline + Tegafuracil + Radiation | Died at 7 months |
| Amel *et al.*[25] | Finger | 5-Flourouracil (for 4 months) followed by doxorubicin + Platinum | Partial response after 4 cycles |
| Morabito *et al.*[26] | Scalp | Methotrexate + Bleomycin | Long term progression free survival |
| Shimato *et al.*[27] | Scalp | Adriamycin + Etoposide | Disease progression after 2 years |

fied a mutation in *PIK3Ca* and *TP53* in two separate hidradenocarcinomas.[29] Of note both hidradenocarcinomas stained strongly for EGFR by immunohistochemistry but neither had EGFR amplification by FISH. Kazakov *et al.* reported a case series of 14 cutaneous HA studied for Her2/neu gene expression and *TP53* mutation analysis.[30] Three specimens had an IHC-score of 2+ for Her2/neu but both were negative by FISH. Also 9 of these cases were studied for TP53 mutations, with two tumors harboring mutations and seven cases remaining wild type. Biernat *et al.* also analyzed *p53* mutation in 16 HA and found that only 30% of the patients carried this mutation.[31]

Formalin fixed paraffin embedded (FFPE) was sent to Foundation Medicine for Foundation One testing using the next generation sequencing in 236 cancer related genes. Four genomic events were identified using the panel from Foundation Medicine including *FGFR1* amplification, *CDH1* splice mutation, *MYST3* amplification *and* ZNF703 amplification. *FGFR1* gene encodes for Fgfr1, which plays key roles in regulation of the cell cycle, survival, migration and angiogenesis, and is an upstream regulator of the *RAS*, *MAPK*, and *Akt* signaling pathways. *FGFR* amplification has been described in various malignancies including breast (11%), pancreatic adenocarcinoma (7%), sarcoma (5%), and lung adenocarcinoma (3.5%).[31,32] Tumors with *FGFR1* amplification may be sensitive to Fgfr family inhibitors including pazopanib, a pan kinase (*VEGFR/PDGFR/FGFR*) inhibitor. FDA approved therapies for this mutation in other tumor types includes pazopanib, ponatinib and regorafenib. *CDH1* encodes the transmembrane protein E-cadherin or CAM 120/80, which plays an important role in epithelial cell-cell adhesion.[33] E-cadherin immunohistochemistry is widely used by the pathologists in the diagnosis of breast cancer. Of note, the mutation in *CDH1* detected in this tumor, 2439+2T>G has not been previously reported and currently there are no targeted therapies for this mutation. *MYST3* encodes a histone lysine acetyltransferase protein most commonly known as MOZ. Genetic rearrangements in *MYST3* have been described in acute myelogenous leukemia, (8;16) (p11;p13) and are associated with the M4 and M5 subtypes.[34] *ZNF703* amplification encodes a transcriptional repressor, which plays a key role in stem cell proliferation.[35] Mutations in *ZNF703* are associated with luminal B breast cancers with aggressive and poor outcome.[36] Currently there is no available target against this mutation as well.

As mentioned above, whole exome sequencing identified mutations in two actionable genes including *PTCH1* and *TCF7L1*. *PTCH1* is a member of the patched gene family and encodes the receptor for sonic hedgehog

(SHH). Mutations in *PTCH1* or the hedgehog pathway are implicated in about 90% patients with basal cell carcinoma (BCC) of the skin.[37] Inhibition of the hedgehog pathway through vismodegib has led to a breakthrough for patients with metastatic or advanced BCC with response and disease control rates of about 45%[38,39] *TCF7L1* encodes a member of the T cell factor/lymphoid enhancer factor family of transcription factors involved in the Wnt signaling pathway.[40] More specifically, *TCF7L1* bound *CTNNB1* (Catenin, beta-1) promotes transcription while unbound *TCF7L1* suppress transcription. *TCF7L1* is necessary for the terminal differentiation of epidermal cells, the formation of keratohyalin granules, and the development of the barrier function of the epidermis. *TCF7L1* based activation has been implicated in the pathogenesis of human breast and colon cancer.[41,42] Whether the specific mutation in *TCF7L1* as reported in this case is functional remains unclear, however, a clinical trial with a Wnt inhibitor would be rational treatment option.

Finally, we would like to make note of the differences between genetic events reported in Foundation Medicine targeted panel and the Baylor Whole Exome analysis. For example, Foundation Medicine sequences *PTCH1* as a part of its panel but *PTCH1* was not called as a mutation. The possibilities for these discrepancies include tissue heterogeneity or difference in techniques in sequencing. In addition, it should be noted that, we did not find a p53 mutation or *HER2* expression as has been demonstrated in previous studies.

## Conclusions

In summary, we are the first to describe the molecular profile in HA, a rare tumor. At present it remains unclear if the mutational profile is clinically relevant. We do want to emphasize that immunohistochemistry has been clinically helpful in this case as this patient has responded to anti-estrogen therapy for greater than one year. Future studies are needed to further characterize the molecular landscape of HA and to determine if these characterizations are clinically relevant.

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