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Favorable response to combined androgen blockade for metastatic cutaneous apocrine carcinoma: a case report

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Introduction: Most cases of cutaneous apocrine carcinoma (CAC) express androgen receptor. Androgen signal is thought to have a relationship on the survival and cell growth of the tumor.

Presentation of Case: A 53-year-old man with a red superficial nodule on the left axilla and a back pain was diagnosed with CAC in the left axilla with multiple bone and bone marrow metastases. After cytotoxic chemotherapy for around 4 years, severe anemia, thrombocytopenia, and disseminated intravascular coagulation progressed. We started combined androgen blockade by bicaltamide and degarelix, and the therapy had successfully maintained stable disease for more than 6 months.

Discussion: Most cases of CAC express androgen receptor. Androgen signal could have a relationship on the survival and cell growth of the tumor.

Conclusion: Antiandrogen therapy for androgen-receptor positive CAC is a promising therapeutic option.

Keywords: Apocrine carcinoma, Androgen receptor, Antiandrogen therapy, Combination androgen blockade, Case report

Cutaneous apocrine carcinoma (CAC) is a rare cutaneous adnexal cancer, occurring in 1 per 10 million people, according to the National Cancer Institute Surveillance, Epidemiology, and End Results (SEER) registry from 1973 to 2006[1]. CAC occurs equally in both sexes (males 52% and females 48%), and the median age of onset is 67 years[1]. CAC often arises in the axilla and anogenital region, which are rich in apocrine glands. The causes and risk factors for CAC have not been clarified. The survival of patients with local/regional disease and metastatic disease has been reported to be 55.0 and 33.0 months, respectively[1].

Most cases are diagnosed as local/regional disease, and they undergo surgical treatment. On the other hand, metastatic CAC is quite rare, and no standard treatment has been established. There are only a few reports of treatment for metastatic CAC. Several case studies described the use of cytotoxic agents including adriamycin, cyclophosphamide, vinblastine, bleomycin, 5-fluorouracil, and methotrexate[2–4], and exploratory treatments such as anti-HER2 antibody[5] and PD-1 blockade were also reported[6].

Increased expression of androgen receptor (AR) has been shown in CAC[7], and androgen signaling is thought to be associated with tumor growth[8]. Although the potential benefit of antiandrogen therapy for CAC has been suggested, there have been no reports of antiandrogen therapy for CAC so far. In addition, while previous reports showed CAC with distant metastasis of lung[2], brain[9] and bone[10], this is the first report of CAC with bone marrow metastasis. This is the first report which showed the efficacy of antiandrogen therapy for CAC.

Case presentation

A 53-year-old Asian man, who had no notable past medical or surgical history, had a 4-year history of a severe back pain. He did not take any medication. He had no notable family history of malignant tumor. In 2015, computed tomography (CT) showed osteoplastic changes of the vertebrae, and fluorodeoxyglucose-positron emission tomography/computed tomography (FDG-PET/CT) showed high FDG uptake by all vertebrae in the previous hospital (**Fig. 1**). He was referred to our hospital for further examination and treatment in 2015. A reddish, flat, and stiff nodule, with a diameter of 3 cm (**Fig. 2**), was observed in his left axilla. No obvious lesions were found in the mammary glands or salivary glands. Peripheral blood examination showed immature white and red blood cells, which suggested bone marrow involvement of the tumor. He had no notable past history and family history. Pathologic examination of a biopsy

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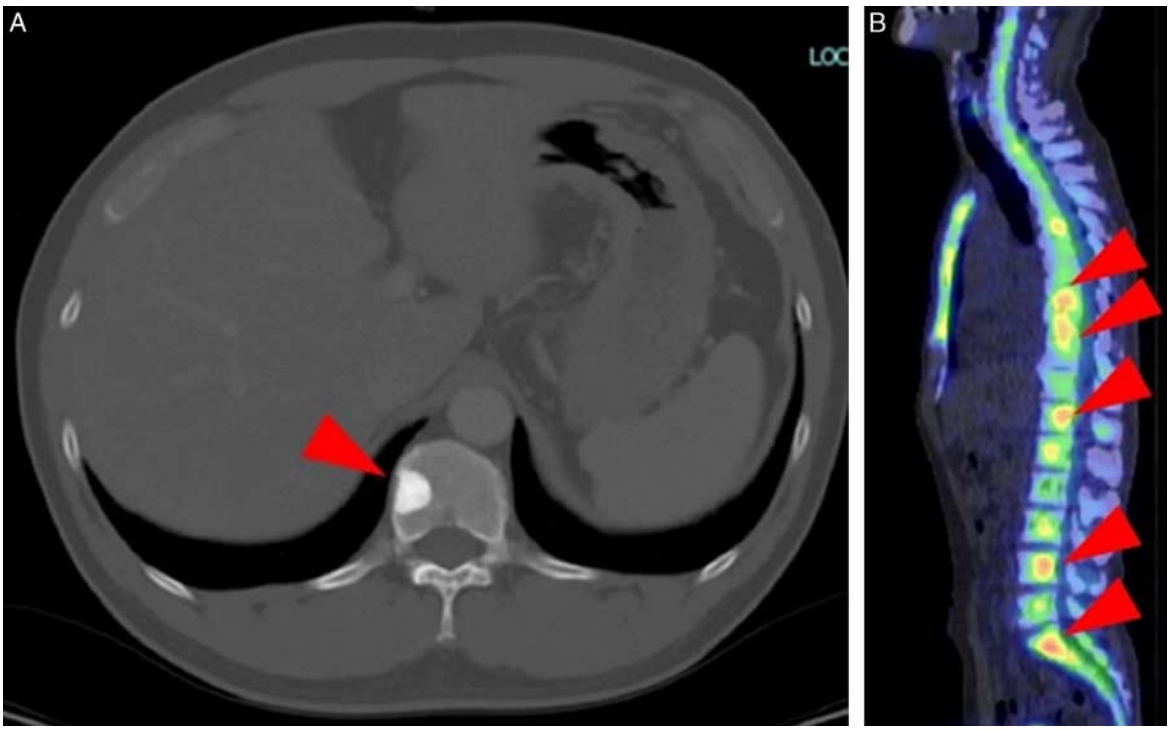

Figure 1. Computed tomography and fluorodeoxyglucose-positron emission tomography (FDG-PET) at the initial diagnosis in 2015. Arrow heads indicate metastatic sites of the spine (A) and high FDG uptake in the spine (B).

specimen of the nodule in his left axilla showed atypical cells having hyperchromatic nuclei and intracytoplasmic mucin in the dermis (**Fig. 3A**). Immunohistochemically, the cells were positive for cytokeratin-7 (CK7), gross cystic disease fluid protein 15 (GCDFP15), and AR (**Fig. 3B**), but negative for CK20, caudal type homeobox 2 (CDX2), thyroid transcription factor 1 (TTF-1), napsin A, estrogen receptor, and progesterone receptor. Human epidermal growth factor receptor 2 (HER2) was score 2+, equivocal, according to the guideline of breast cancer in 2013[11]. These features suggested carcinoma with apocrine differentiation. Bone marrow biopsy showed carcinoma cells having eosinophilic cytoplasm and intracytoplasmic mucin with a glandular cavity structure, which suggested bone marrow metastasis of apocrine carcinoma (**Figs. 3C, D**). Because of those pathologic features and the finding that no lesion was found in other regions such as the mammary glands or salivary glands, he was finally diagnosed with CAC with bone and bone marrow metastases.

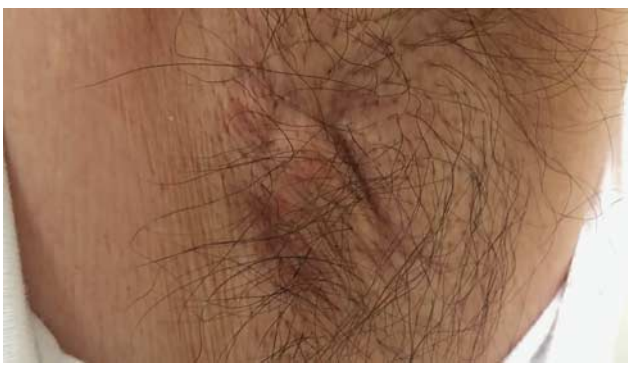

Figure 2. The superficial nodule on the left axilla.

The patient received tegafur/gimeracil/oteracil (S-1) treatment as a first-line therapy, and the disease was well controlled for 3 years. However, the treatment was changed to paclitaxel because of worsening anemia and thrombocytopenia. No significant change of the primary left axillary nodule was observed. After 7 months, anemia and thrombocytopenia caused by bone marrow metastases gradually progressed, and he needed transfusion of red blood cell and platelet components due to severe anemia (hemoglobin 4.7 g/dL) and thrombocytopenia (platelets $1.3 \times 10^4/\mu L$). The blood examination also showed evidence of disseminated intravascular coagulation (DIC) (fibrinogen 205 mg/dL, prothrombin time-international normalization ratio (PT-INR) 1.24, fibrin/fibrinogen degradation products (FDP) 41.9 μg/mL, D-dimer 11.4 μg/mL), suggesting progression of bone marrow metastases. He was admitted to our department for third-line treatment in April 2019. His Eastern Cooperative Oncology Group performance status was 2. It was thought that he would not be able to tolerate cytotoxic chemotherapeutic agents. The genomic profiling examination (FoundationOne CDx assay; Foundation Medicine, Inc. Massachusetts) showed the activating mutation of *PIK3CA* gene, but no therapeutic options, including a clinical trial targeting *PIK3CA* mutation, were available.

Because the tumor was positive for AR, and there were some previous reports of the efficacy of antiandrogen therapy for AR-positive tumors, antiandrogen therapy was started. With the patient's written, informed consent, antiandrogen therapy using bicaltamide (80 mg per day, orally, continuous administration) and degarelix (240 mg every 4 weeks, subcutaneously) was initiated. Fourteen days after the initiation of the therapy, the anemia and thrombocytopenia

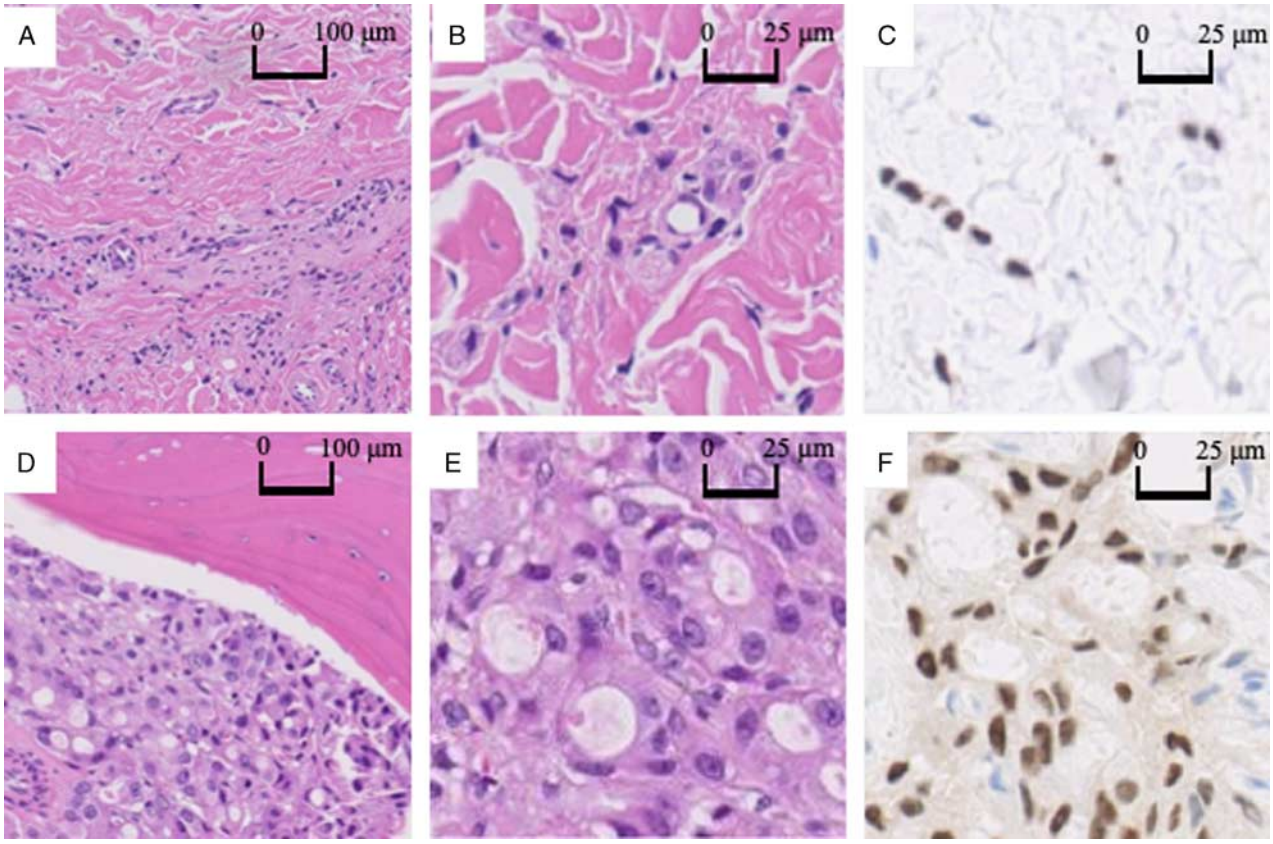

Figure 3. Histologic examination of the primary and metastatic site of the tumors. A, Hematoxylin and eosin (HE) staining of the primary tumor of low-magnification power (×10). B, The same micrograph as (A) of high-magnification power (×40). C, Immunostaining with anti-androgen receptor of the primary tumor. D, HE staining of the bone marrow metastasis of low-magnification power (×10). E, The same micrograph as (D) of high-magnification power (×40). F, Immunostaining with antiandrogen receptor of the bone marrow metastasis.

improved, to the extent that he did not need transfusion. His DIC status also improved (fibrinogen 253 mg/dL, PT-INR 1.06, FDP 19.6 μg/dL, D-dimer 4.0 μg/dL), which strongly indicated a therapeutic response of the bone marrow metastases. He had an adverse event, an injection site reaction of grade 1 in the Common Terminology Criteria for Adverse Events (CTCAE). He has now been treated with the antiandrogen therapy for more than 6 months, without worsening of the anemia, thrombocytopenia, and DIC status. This case report is reported in line with the SCARE 2018[12].

Discussion

CAC is one of the adenocarcinomas originating from apocrine glands that mainly arises in the axilla and anogenital region, which are rich in apocrine glands. Although apocrine gland adenocarcinoma is reported to have a relatively nonaggressive nature, lymph node metastasis is found in 40%–50% of the patients at initial diagnosis[13,14]. Some reports showed that extranodal metastasis is rarely observed[14,15], but liver, lung, and bone marrow metastases are known to occur[13,14]. Because metastatic CAC is rare, no standard treatment has been established. Several case reports and case series have described treatment for metastatic CAC using cytotoxic drugs[2–4], anti-HER2 antibody[5], and PD-1 inhibitor[6].

The present case had CAC with bone and bone marrow metastases that caused severe anemia, thrombocytopenia, and DIC. Cytotoxic chemotherapy agents, S-1 and paclitaxel, had been administered for ~4 years and provided disease control for a certain period. However, the patient developed drug resistance. Continuation of cytotoxic drugs was not suitable because of his life-threatening anemia and thrombocytopenia. Since antiandrogen therapy has less risk of myelosuppression, it was thought that the patient was more likely to tolerate it than cytotoxic drugs. The patient successfully recovered from the severe condition caused by bone marrow metastases of CAC without any particular critical adverse events of antiandrogen therapy.

Androgens such as testosterone are secreted mainly from the testes, and some are also secreted from the adrenal glands. Androgens function on target organs such as the prostate via the binding to ARs. Antiandrogens suppress the action of androgens in target organs[16]. Luteinizing hormone-releasing hormone antagonists inhibit LH secretion from the pituitary gland and subsequently inhibit testosterone secretion from the testes. Androgen antagonists inhibit the activity of androgen from both testes and adrenal glands. Combination androgen blockade (CAB) using a nonsteroid antiandrogen bicaltamide and an luteinizing hormone-releasing hormone antagonist degarelix inhibits the activity of androgen secreted both from the testes and the adrenal glands. The efficacy of CAB was assessed in the treatment of prostate cancer, and a benefit of CAB compared with castration alone was shown in a meta-analysis[17]. Therefore,

hormonal therapy such as CAB is recognized as the first-choice systemic therapy for metastatic prostate cancer. Because the AR has been reported to be expressed in 60%–85% of breast cancers[18] and salivary duct carcinoma[19–21], there have been several studies of antiandrogen therapy for AR-positive cancers other than prostate cancer. A phase II study of bicalutamide for 26 AR-positive, estrogen receptor-negative metastatic breast cancer patients showed that 19% of them maintained stable disease for more than 6 months[22]. A phase II study of CAB for 36 AR-positive salivary gland carcinoma patients showed that the response rate was 41.7%, and median overall survival was 30.5 months[23]. No serious adverse events were reported in both studies. Although no comparisons between antiandrogen therapy and chemotherapy have been reported, the efficacy and safety of CAB for AR-positive tumors have been suggested.

The AR is expressed not only in normal prostate glands and salivary glands, but also in normal apocrine glands. Similar to the functional role of androgens in the prostate gland, androgens have also been suggested to modulate normal apocrine gland function[24]. Therefore, AR-expressing CACs might be sensitive to antiandrogen therapy because of the dependency on androgen for their growth or maintenance. The efficacy of hormonal therapy including CAB varied according to the origin of AR-positive tumors. This is possibly because tumor cell growth and survival might depend on AR-signaling differently. AR-positive cases have been reported to account for 64%–100% of CAC cases[7,25,26]. The present patient also had AR-positive CAC, and CAB showed obvious efficacy without serious adverse events.

Conclusion

In the present study, antiandrogen therapy for a patient harboring AR-positive CAC with bone and bone marrow metastases resulted in a good clinical course. Although there was no previous case report that showed favorable results of hormonal therapy for CAC, this is the first report demonstrating the efficacy and safety profile of antiandrogen therapy for AR-positive CAC. Further analyses of this therapy are needed to establish a standard treatment strategy for AR-positive CAC.

Ethical approval

Written informed consent was obtained from the patient for induction of the therapy and publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

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Author contribution

T.I. have contributed to treatment of the patient and writing the manuscript. M.I., Y.S., K.T., H.A., H.K., and K.A. contributed to supervise the treatment of the patient. H.Y. and Y.O. contributed to pathological diagnosis. E.B. is a corresponding author and contributed to supervise the treatment and the writing of the final manuscript.

Conflict of interest disclosure

E.B., the corresponding auther, received speaker's bureau and grant from Takeda Pharma and Daiichi Sankyo. The remaining authors declare that they have no financial conflict of interest with regard to the content of this report.

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Guarantor

The guarantor is that individual who accepts full responsibility for the work and/or the conduct of the study, had access to the data, and controlled the decision to publish.

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