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Review

Chemotherapy of Rare Skin Adnexal Tumors: A Review of Literature

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Abstract. *Malignant skin adnexal tumors are rare neoplasms which are derived from adnexal epithelial structures of the skin: hair follicle, or sebaceous, apocrine or eccrine glands. Among them, eccrine porocarcinoma is the most frequent, with an aggressive behavior compared to other more common forms of non-melanoma skin cancer. Only few reports describe the treatment of metastatic adnexal tumors, and there is no consensus about the better strategy of chemotherapy. Given the few cases and the absence of randomized clinical trials, it is important to collect clinical experiences on these tumors. Most of these adenocarcinomas are very aggressive and also chemoresistant, and only a targeted-therapy could have an impact on patient survival. Therefore, further studies on the biology of these diseases are necessary. The purpose of the present review is to discuss the treatment of malignant neoplasms of cutaneous adnexae and to suggest some future therapeutic options based on targeted-therapy.*

Skin adnexal tumors (SATs) represent a group of rare benign or malignant epithelial skin tumors of the adnexal epithelial structures of the skin, *i.e.* hair follicle, or sebaceous, apocrine or eccrine glands (1).

Many sweat gland tumors have both eccrine and apocrine origin, among these are hydrocystoma, poroma, cylindroma, spiradenoma and chondroid syringoma. Hamartomas also are mixed tumors, composed of eccrine and apocrine constituents (2).

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Malignant SATs are a large group that represents the most challenging area of dermatopathology, in particular for eccrine and apocrine adenocarcinomas; these kinds of tumors present a bewildering array of morphologies that often defy precise classification (3). The correct identification of the origin of a tumor is important for the determination of the most appropriate therapy and prognosis (2, 3). Benign neoplasms only need a local excision and most do not carry a risk of local relapse, but they might be markers for syndromes associated with internal malignancies.

Malignant eccrine neoplasms are rare, representing only 0.005% of all skin tumors. These tumors are not often diagnosed clinically, or are misinterpreted as soft tissue neoplasms. Their prognosis is usually poor. In fact, there are no current uniform treatment guidelines, especially for metastatic disease (4). Successful chemotherapy and radiotherapy have been documented only in isolated case reports of metastasizing hydradenocarcinomas and eccrine carcinomas (5-7).

Eccrine carcinoma or porocarcinoma (EPC) is common in patients more than 60 years old, with no particular sex predilection (8, 9). Approximately 250 cases of eccrine porocarcinoma have been reported since this disease was first described in 1963, under a variety of names such as dysplastic poroma, malignant syringoacanthoma, malignant eccrine poroma, malignant hydroacanthoma simplex, and poroepithelioma (10). Although some cases have been reported to be consequent to long radiotherapy, the etiology of the majority of these tumors remains unknown (11). This neoplasia demonstrates the most aggressive behavior among SATs and compared to other types of non-melanoma skin cancer. EPC has a propensity to arise on the lower limbs (44%), trunk (24%), or head and neck regions (24%); other common sites include the face, scalp and ears (about 20%), upper extremities (about 11%), abdomen (about 9%) and genital sites (12). Furthermore, rare cases of penile involvement have also been reported (13).

EPC usually appears as a single nodule or a plaque arising from a pre-existent eccrine poroma, or developing *de novo*. Two EPC histopathological variants are described: trabecular or epidermotropic; this latter form is more aggressive, leading to frequent local recurrences and metastases (14).

EPC tumors can be of different size at diagnosis, from less than 1 cm up to 10 cm, and their morphological features can be nodular, infiltrative, ulcerated or polypoid. Multinodularity, ulceration and rapid growth may be associated with both local recurrence and metastasis (15). A long clinical history is often encountered (up to 50 years) because some of these tumors can derive from a pre-existing benign eccrine poroma. EPC has a mortality rate of 67% when regional lymph nodes are involved, and the mean time from initial presentation to treatment is 8.5 years (16).

The clinical differential diagnosis among SATs includes seborrheic keratosis, pyogenic granuloma, amelanotic melanoma, squamous cell carcinoma, basal cell carcinoma, verruca vulgaris, and metastatic adenocarcinoma (12). Clinically, SATs must be taken into consideration in the differential diagnosis of patients older than 50 years with diagnosis of Paget's disease, melanoma, or inflammatory, lymphocytic and vascular lesions (17,18). Regional lymph node metastases can be found in about 20% of the patients, and distant metastases can arise in about 10% (15).

There are only few reports describing the treatment of SATs, and there are no uniform guidelines. The clinical experience described in published case reports is the only source of available information. The treatment-of-choice is wide local excision with a surgical margin of 1 to 2 cm, with clearance of draining lymph nodes, but for metastatic or inoperable disease, systemic treatment is needed.

Treatment modalities include Mohs micrographic surgery, chemotherapy and radiation therapy. Mohs micrographic surgery can be used in functionally- or cosmetically-limiting locations. Lymph node involvement has been reported in approximately 50% of cases, especially in those with poorly differentiated tumors, hence sentinel lymph node biopsy has begun to be investigated as a staging tool (19,20). Particularly in cases of tumor with poor prognostic features, showing a propensity for nodal involvement, wide-margin excision and sentinel lymph node evaluation are recommended (21).

However, prophylactic lymph node resection does not appear to improve disease-free survival.

Adjuvant radiation can be useful in high-risk cases (tumors larger than 5 cm, positive surgical margins of 1 cm, moderately- to poorly-differentiated histology with lymphovascular invasion) (22). Radiotherapy of the involved lymph nodes is recommended when there is extranodal extension or when more than four nodes are involved (23). Whole-brain radiotherapy and gamma knife surgery for brain metastasis is described, with poor results (24).

All authors agree that the role of chemotherapy in the treatment of SATs remains unclear. In fact, SATs are considered relatively chemoresistant, although some responses to single-agent or combined chemotherapy have been reported.

The association of two or three chemotherapeutic agents has led to some responses in metastatic disease, although these therapy schedules are characterized by short-term duration and great toxicity. A case of metastatic sweat gland carcinoma with distant lesions to lung and bone, treated with nine cycles of doxorubicin, mitomycin, vincristine, and 5-fluorouracil followed by maintenance therapy with cyclophosphamide, vincristine, and 5-fluorouracil has been described: the patient obtained a complete response to the treatment, lasting 16 months (25). In another case report, the duration of response was two years with a treatment based on anthracycline, cyclophosphamide, vincrisine and bleomycin, while a combination of cyclophosphamide, anthraciclyne and tegafur together with radiotherapy led to a short-term response in other reports (26). Orphan *et al*. described cases with good responses to 5-fluorouracil, thiotepa and cyclophosphamide (27, 28). Four cases of pediatric EPC were treated with a combination of 5-fluorouracil, doxorubicin and cyclophosphamide, hovewer, no response was observed one year after therapy (29).

Experiences with cisplatin and 5-fluorouracil or cisplatin and cetuximab are reported, but with discouraging results (30-31); while carboplatin and paclitaxel led to a prolonged remission in a single experience with a patient with multi-metastatic disease (22).

Barzi *et al*. proposed a new protocol that utilized isotretinoin (13-cis retinoic acid) and interferon-alpha to treat metastatic EPC, with promising results (11). Anti-EPC activity has also been reported using interferon-alpha alone or in combination with isotretinoin and 5-fluorouracil, administered by intra-arterial infusion, in combination with melphalan and regional hyperthermia (27). Anthracycline-based chemotherapy regimens also resulted in complete and partial responses in other case reports. A complete response lasting for 16 months and prolonged survival was obtained with the combination of doxorubicin, mitomycin C, vincristine and cisplatin in a patient with an eccrine porocarcinoma with bone and visceral metastases (32). Single-agent treatments such as docetaxel, paclitaxel, and 5-fluorouracil have demonstrated some antitumor activity in metastatic EPC: partial response to docetaxel monotherapy in a patient previously treated with epirubicin (33), and long-term stable disease in a patient treated with a combination of interferon-alpha and weekly paclitaxel have been reported (25).

Recently, an article highlighted the role of second-line taxanes in platinum-resistant or patients with refractory metastatic EPC (34). However, other studies have described cases showing no clinical response to the same chemotherapy (28).

Our Medical School reported a unique case (35, 36) of a 57-year-old female affected by a large perineal eccrine porocarcinoma with wide local invasion who underwent a Miles abdominoperineal resection with colostomy, total hysterosalpingo-oophorectomy en bloc, an extended colpo-vulvectomy with a wide cutaneous excision of the tumor with an excision margin of 2 cm, including the anus, distal urethra, and external meatus (pT4 N0 Mx). The patient was not submitted to any radiochemotherapy. The patient follow-up had been negative for four years, when magnetic resonance imaging revealed a neoplastic lesion measuring approximately 5 cm in diameter, with irregular borders and infiltration into the adjacent tissues of the left inguinal region. The patient started a combined chemotherapy with 5-fluorouracil, cisplatin and docetaxel and underwent a single-fraction radiation therapy for a vertebral collapse. But the patient died due to neoplastic cachexia several months later. This aggressive EPC showed no response to any treatment and intrinsic chemoresistance.

EPC is a rare tumor of sweat glands with a high local recurrence rate and tendency to metastatic spread. No standard therapy protocols for metastatic and locally advanced disease exist. We herein report the therapeutic strategies for cases of metastatic SATs, with particular attention to EPC, described in the literature (Table I). Our suggestion is that these chemoresistant tumors can benefit only from a targeted-therapy.

As far as the immunohistochemical expression of specific markers is concerned, the cells of eccrine sweat glands express low and high molecular weight keratins, epithelial membrane antigen (EMA), carcinoembryonic antigen (CEA), S100 protein, smooth muscle actin (SMA), p63, calponin, cytokeratin 14 and B-cell lymphoma-2 (BCL2) (2). Some eccrine carcinomas express estrogen and progesterone receptors, which have important clinical implications for hormone therapy. When eccrine carcinomas exhibit positive immunohistochemical staining for estrogen and progesterone receptors, the differential diagnosis from cutaneous metastasis of breast cancer is very difficult (2, 3). Androgen receptor evaluation is very important in the differential diagnosis between these two tumor types since these receptors are typically expressed at a higher frequency in metastatic breast cancer and are expressed only in a subset of SATs (37). Detection of epidermal growth factor receptor can be useful because it is expressed in more than 81% of SATs, but only in 17% of metastatic breast carcinoma (38). Human epidermal growth factor receptor-2 (HER2) is expressed in only 3.5% of SATs, while it has higher frequency in breast cancer (20% of all breast neoplasms) (39). Together with immunostaining for these receptors, detection of cytokeratin (CK) 7, p63, and CK 5/6 is very important for differential diagnosis between SATs and breast cancer, and for performing therapy (40, 41). In fact, SAT cells are usually strongly-positive for p63 and CK 5/6, while metastatic breast cancer does not express these; yet CK 7 has a specific focal pattern in SATs, while it has a diffuse pattern in metastatic breast cancer (40, 41).

The molecular pathogenesis of malignant adnexal tumors is still not well understood. Since it was first described, only little information about molecular alterations in EPC have been discovered. Gu *et al*. described overexpression of p16 protein as a common feature in EPC (42). P16 and retinoblastoma protein (Rb), are tumor-suppressor proteins that regulate the G_1/S cell-cycle checkpoint: their inactivation allows the cell to enter the S phase after a short break at the G_1 checkpoint. In metastatic EPC, p16 overexpression is associated with loss of RB function, since RB protein can induce transcriptional down-regulation of p16. Gu *et al*.'s study suggested that aberration in the p16/RB pathway can be associated with accelerated tumor proliferation, poor prognosis and tumor recurrence (42).

The positive expression of Ki-67 and p53 can help differentiate benign from malignant tumors (40). Akalin *et al*. also demonstrated *p53* mutations related to EPC. P53 is a tumor-suppressor protein that regulates cell growth; its mutations and loss of function are involved in the carcinogenetic pathway of EPC, but are not sufficient for its development. Therefore, aberrant p53 expression cannot be accepted as a valuable parameter for malignancy without other oncogene alterations (43). It is interesting that mutations in phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha (*PIK3CA*) and *p53*, expressed by a subset of metastasizing SATs, are also frequently present in breast cancer. Targeted-therapy, including PI3K pathway inhibitors, could be a potential treatment for rare cases of SATs with metastases, and further investigations are needed (44).

Due to the described analogies between breast carcinomas and SATS, using the same chemotherapeutic agents and the same targeted therapy can be effective. Only one successful case of anti-hormonal therapy of eccrine gland tumors is described: a patient with distal metastasis secondary to an eccrine tumor responded well to tamoxifen (45). Therefore, an anti-estrogen therapy in metastasizing SAT with positive hormone receptor immunohistochemistry should be taken into consideration (46, 47).

Only two experiences of treatment with a targeted therapy for metastatic SATs are described. The first is with sunitinib, an oral tyrosine kinase inhibitor; its efficacy in adnexal carcinomas was recently reported in two cases. Certainly, sunitinib should be considered in further studies of these rare tumors (48). The second clinical experience is with lapatinib, an oral anti-HER2 targeted-therapy, successfully utilized for a patient with metastatic apocrine carcinoma (49).

Table I. *Therapy protocol for metastatic skin adnexal tumors/eccrine porocarcinoma (SAT/EPC).*

Reference	Age, years	Gender	Site of SAT/EPC	Lymph node metastasis	Distant metastates	Treatment		
						Surgical	Radiation	Chemotherapy
Kurashige *et al*. (51)	50	M	Left arm	+	+	+	21 Gy	Docetaxel, cisplatin
Toshiko *et al*. (52)	80	M	Left palm	–	+		Data not available	
Landa *et al*. (53)	24	M	Left leg	+	–		Data not available	
Rehal *et al*. (54)	87	M	Left temple	–	+		Data not available	
Kurisu *et al*. (55)	78	F	Left ingiunal skin	–	+	+	–	-
Baroni *et al*. (56)	73	M	Right toe	+	–	+	–	+ (Unknown)
Vleugels *et al*. (20)	59	F	Ventral forearm	+	–	+	54 Gy	-
Ramirez *et al*. (57)	69	F	Right leg	+	+		Data not available	
Marone *et al*. (6)	42	M	Left arm	+	–	+	–	Bleomycin, electrochemotherapy.
Ishida *et al*. (58)	72	M	Right thigh	+	+	+	–	Carboplatin, farmorubicin
Kim *et al*. (59)	42	M	Right palm	+	+	+	Gamma knife	Cyclophosphamide, cisplatin, doxorubicin
Shiohara *et al*. (28)	62	F	Head	+	+	+	50 Gy	Cisplatin, adriamycin, VDS
Shiohara *et al*. (28)	64	M	Leg	+	–	+	30 Gy	Mitomycin, vincristine, epirubicin
Shiohara *et al*. (28)	79	F	Leg	+	+	+	30 Gy	-
Shiohara *et al*. (28)	66	F	Foot	+	+	+	–	-
Shiohara *et al*. (28)	81	F	Buttock	+	+	–	-	Cisplatin, 5-FU
Gutermuth *et al*. (25	67	M	Left lateral neck	+	–	+	–	INFα, paclitaxel
Ameen *et al*. (60)	53	M	Right foot	+	+	+	–	-
Gonzalez- Lopez *et al*. (61)	71	M	Right thigh	+	+	+	45 Gy +55 Gy	Isotretinoin, tegafur
Lan *et al*. (62)	81	F	Face	–	+	–	-	-
Goel *et al*. (63)	42	M	Right foot	+	+	+	Data not available	
Magdum *et al*. (64)	57	M	Brain	–	+	+	Data not available	
Plunkett *et al*. (33)	45	F	Breast	+	+	+	–	Epirubicin, docetaxel
Biondi *et al*. (65)	52	M	Mandibular region	+	+	+	–	Cisplatin, doxorubicin, cyclophosphamide
Permal *et al*. (66)	67	F	Left thigh	–	+	+	–	Tamoxifen
Grimme *et al*. (67)	47	M	Head	–	+	+	44 Gy	IL2, carboplatin, bleomycin, 5-FU
Huet *et al*. (68)	55	M	Scrotum	–	+	+	Carbon dioxide-laser	IFNα
Salvi *et al*. (37)	57	F	Perineal	+	+	+	–	5-FU, cisplatin, docetaxel

F: Female; 5-FU: 5-fluorouracil; IFNα: interferon-alpha; IL2: interleukin-2; M: male; VDS: Vindesine; +: positive; –: negative.

Conclusion

Metastatic SATs are rare and aggressive tumors which have the potential for distant metastasis and are very resistant to conventional chemotherapies. Longer follow-up and several clinical trials are necessary to evaluate new therapeutic strategies in relation to new possible targets. Considering the differential diagnosis between a primary SAT and a secondary neoplasm, skin metastasis of breast cancer is very difficult, hence we suggest the utilization of all available immunohistochemical markers, additionally to clinical and radiological evaluations (50). Yet, due to the sharing of some molecular alterations in breast cancer and SATs, we suggest that using the same chemotherapeutic agents and the same target therapy for metastatic SAT could be effective, considering also the high rate of chemoresistance of these types of neoplasms.

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