Metastatic eccrine carcinoma with stomach and pericardial involvement

Ahmed-Tarig Ahmed, MD,[a] Mohammed A Elkhouly, MD,[b] and Shweta Gupta, MD, FACP[a]

[a]Division of Hematology-Oncology and [b]Internal Medicine Department, John H Stroger Jr Hospital of Cook County, Chicago, Illinois

Skin adnexal tumors (SAT) are rare tumors that make up about 1%-2% of all cutaneous malignancies. They represent a various group of benign and malignant tumors that arise from skin adnexal epithelial structures: hair follicle, pilosebaceous unit, and apocrine or eccrine sweat glands. Although this derivation provides a practical basis for classification, some tumors may exhibit a mixed or more than one line of differentiation, rendering precise classification of those neoplasms difficult, and such cases should be categorized according to prevailing phenotype. In this report, we present a patient with metastatic eccrine carcinoma. Clinical experience for metastatic disease treatment is derived from a few reports, and there are no universal treatment guidelines. Given the few reported cases and the absence of randomized clinical trials for these patients, it is important to collect clinical experiences.

Case presentation and summary

A 56-year-old African man presented with a 5-week history of multiple nontender subcutaneous skin nodules all over his body except for his palms and soles, and associated with generalized itching. He had a mass in the sole of his right foot 35 years previously in another country. The mass had recurred 15 years later and was excised again. The exact etiology of the mass was unknown to the patient. He had no other medical problems. He was on no medications and did not smoke, drink, or use recreational drugs.

His vital signs on admission were normal. Examination was significant for innumerable superficial skin nodules in the scalp, back, torso, and abdomen. The largest was in the neck and measured 4 x 2 cm. A firm right inguinal mass of 7 x 4 cm was palpable. An abdominal exam revealed large ascites but no organomegaly.

The results of laboratory tests were significant for hyponatremia 126 mEq/L (normal, 135-145), hypercalcemia of 12.2 mg/dL (8.5-10.5), with normal phosphorous of 2.5 mg/dL (2.5-4.5), parathyroid of 11.5 pg/ml (6-65), and low vitamin D level of <7 ng/ml (30-100). Other test results were: carcinoembryonic antigen (CEA), 4.36 ng/ml (0.00-2.99); alpha fetoprotein, 2.39 IU/ml (0.00-9.0); calcium 11.6 mg/dL (8.5-10.2); lactate dehydrogenase, 325 U/L (85-210); aspartate aminotransferase, 59 U/L (0-40); alanine aminotransferase 43 U/L (5-35); alkaline phosphatase, 65 u/L (50-120); albumin, 2.7 g/dL (3.8-5.2); white blood cell count, 14.1 k/uL (4.4-10.6); hemoglobin, 12.6 g/dL; and platelets, 339 k/uL (161-369).

A chest and abdomen computed-tomography scan on presentation showed presence of innumerable subcutaneous and intramuscular nodules throughout the chest, abdomen, and pelvis (Figure 1). Extensive peritoneal carcinomatosis in addition to moderate ascites and perivascular lymphadenopathy were evident in the abdomen cuts. Remarkably, multiple lytic, osseous metastases were seen with subacute pathologic fracture of right fourth rib in addition to mediastinal lymphadenopathy with small pericardial effusion in the chest cuts. The right thigh mass was described as a large lobulated solid and cystic mass. Ascitic fluid analysis was negative for malignant cells. Biopsy of one the skin nodules in the upper back showed carcinoma involving the skin with focal tubular differentiation (Figure 2).

Immunohistochemical stains were positive for p63, epithelial membrane antigen, high molecular weight keratin, and p40. The lesional cells were negative for CEA, bcl-2, Ber-Ep4, CK7, and CK20. The profile was compatible with a skin adnexal carcinoma of sweat gland origin. The groin lymph node showed eccrine acrospiroma.

The patient underwent an upper endoscopy to

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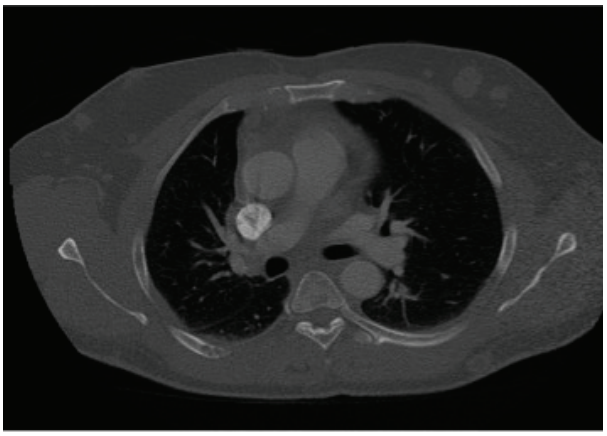

FIGURE 1 A chest and abdomen computed-tomography scan (axial view) shows innumerable subcutaneous and intramuscular nodules throughout the chest. Arrow indicates one of the nodules.

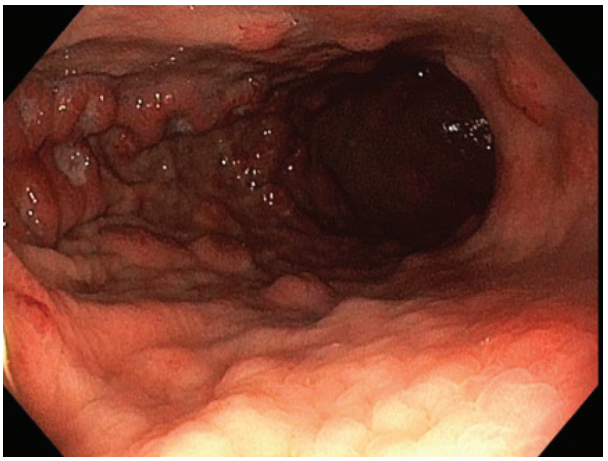

FIGURE 2 Endoscopy: shows the stomach with numerous ulcerated nodules

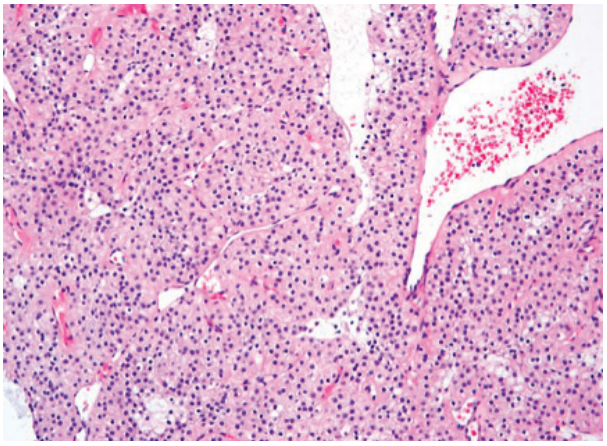

FIGURE 3 A biopsy of one the skin nodules in the upper back shows carcinoma involving the skin with focal tubular differentiation (H&E stain, 4x).

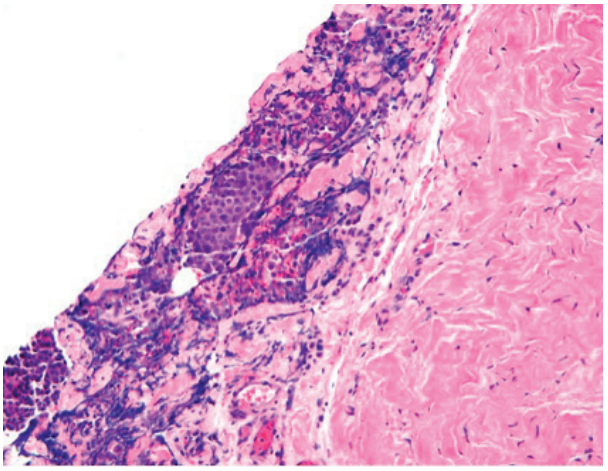

FIGURE 4 An nalysis of the pericardial fluid showed metastatic carcinoma (H&E stain, 4x).

assess for recurrent vomiting and it revealed diffuse areas of large erythematous ulcerated nodules noted in the cardia, fundus, and body of the stomach (Figure 3). A biopsy of the gastric nodules revealed gastric mucosa with metastatic carcinoma.

After a thorough review of the literature, he was started on palliative chemotherapy 13 days after initial presentation with docetaxel 75 mg/m^2, carboplatin AUC 5 (470 mg), and 5-FU (5-fluorouracil, 750 mg/m^2) over 24 hours on days 1 through 5. However, on day 2 of the chemotherapy, he became hypotensive and was found to have cardiac tamponade. He underwent an emergent pericardial window procedure. Analysis of the pericardial fluid was consistent with metastatic carcinoma (Figure 4). Chemotherapy was discontinued while he remained hypotensive requiring multiple vasopressors. His clinical condition did not improve and he passed away 27 days from initial presentation.

Discussion

Sweat gland carcinomas are very rare malignant tumors of the adnexal epithelial structures of the skin, sebaceous, hair follicle, apocrine or eccrine glands that were first described by Cornil in 1865.[1] They occur primarily in adult patients, with a peak incidence in fifth and sixth decades of life.[2,3] The etiology is unknown, but some cases have been reported to be a consequence of radiation therapy.[4] They are almost always an incidental histologic diagnosis.[2,5] The tumors usually appear as single nodule, and multinodularity usually associated with both local and metastatic disease.[6] There are no characteristic findings to suggest that a particular nodule may represent sweat gland carcinoma,

TABLE Previous case reports in the literature

Reference	Age, y	Sex	Primary tumor location	Systemic therapy	OS, mo	Site of metastases
De Iuliis[7a]						
Kurashige	50	M	Arm	Docetaxel, cisplatin	8	Bone
Toshiko	80	M	Palm	Data not available	NR	NR
Rehal	87	M	Temple	Opted for hospice	NR	Lung, bone, hilar, mediastinal nodes
Kurisu	78	F	Inguinal area	Data not available	2	Lung
Ramirez	69	F	Leg	Data not available	NR	Carcinomatous lymphangitis
Ishida	72	M	Thigh	Carboplatin, farmorubicin	NR	Liver, supraclavicular nodes
Kim	42	M	Palm	Cyclophophamide, cisplatin, doxorubicin	NR	Brain, bone, pleura, spinal cord
Shiohara	79	F	Head	Cisplatin, adriamycin, vindesine	27	Bone
Shiohara	66	M	Leg	Mitomycin, vincristine, epirubicin	4	Bone
Shiohara	81	F	Buttock	Cisplatin, 5-FU	40	Bone, pleura
Ameen	53	M	Foot	Did not receive chemotherapy, died of sepsis	NR	Liver, duodenal mucosa
Lan	81	F	Face	Data not available	NR	Extensive cutaneous
Goel	42	M	Foot	Interferon alfa, isotretinoinboplatin, paclitaxol, vincristine, irinotecan	24	Brain, lung, liver
Magdum	57	M	Brain	Data not available	NR	Brain
Plunkett	45	F	Breast	Epirubicin, docetaxel	NR	Lung
Biondi	52	M	Mandibular area	Cisplatin, doxorubicin, cyclophophamide	NR	Pericardium
Permal	67	F	Thigh	Tamoxifen	NR	Lung
Grimme	47	M	Head	Interleukin-2, carboplatin, bleomycin, 5-FU	6	Liver, bone, kidneys
Salvi	57	F	Perineal area	5-FU, cisplatin, docetaxel	NR	NR
Battistella[24]	64 43	M W	Shoulder Scalp	1st-line cisplatin+5-FU; 2nd-line sunitinib 1st-line carboplatin+paclitaxel; 2nd-line sunitinib	21 13	Lung Vertebral spine
Hidaka[25]	62	M	Scalp	Traustuzumab	NR	Liver
Mandaliya[26]	66	F	Forearm	Concurrent cisplatin, docetaxel	NR	Mediastinum
De Bree[27]	69	M	Thigh	Topical 5-flurouracil and docetaxel	NR	Bone
Bahi[28]	50	W	Left arm	Methotrexate	NR	Lung
Wang[29]	35	W	Right shoulder	Cisplatin+vinorelbine	NR	Lung
Our patient	56	M	Upper back	Docetaxel, cisplatin, 5-FU	<1	Pericardium, stomach

5-FU, fluorouracil; NR, not reported; OS, overall survival

[a]The article by De Iuliis et al, Reference 7, is a review and the case reports from Kurashige to Salvi, as listed in the table, were featured in the De Iuliis article.

and even if sweat gland tumor is suspected, benign counterparts are more common.

Eccrine carcinoma is the most aggressive among skin adnexal tumors. They can arise on the lower limbs, trunk, head and neck, scalp and ears, upper extremities, abdomen, and genital sites.[7]

The cells of eccrine sweat glands express low molecular weight keratin, epithelial membrane antigen, carcino-

embryonic antigen, as well as S100 protein, smooth muscle actin, p63, calponin, cytokeratin 14, and bcl-2.[8] Skin tumors with eccrine differentiation may stain for estrogen and progesterone, which has important clinical implications because those patients can be treated with hormonal therapy.[9] Positivity for estrogen receptors does not differentiate cutaneous eccrine tumors from cutaneous metastases of breast cancers.[8,9] Androgen receptor evaluation in these cases can help distinguish between the two.[10] Human epidermal growth factor receptor 2 (HER-2) is expressed in 3.5% of skin adnexal tumors.[11]

The molecular pathogenesis of malignant adnexal tumors is not clear, but overexpression of tumor suppressor protein p16 has been described as a common feature in eccrine carcinomas.[12]

Prognostic factors for sweat gland carcinoma are difficult to identify, because of the small number of reported cases. The likely prognostic factors include size, histological type, lymph node involvement, and presence of distant metastasis. Absent of lymph node involvement correlates with 10-year disease-free survival rate of 56%, which falls to 9% if nodes are involved.[13]

There are no uniform guidelines for the treatment sweat gland carcinomas, and the clinical experience described in the literature is the only source of available information.

The treatment of choice of all subtypes of localized sweat gland carcinomas is wide surgical excision with broad tumor margins, given the propensity for local recurrences along with regional lymph node dissection in the presence of clinically positive nodes. Prophylactic lymph node resection does not seem to improve survival or decrease recurrence rates.[7] The use of adjuvant radiotherapy to prevent local recurrence also is not well established. One report suggested radiosensitivity of these tumors, and adjuvant radiation was therefore recommended in high-risk cases (ie, large tumors of 5 cm and positive surgical margins of 1 cm) and moderate to poorly differentiated tumors with lymphovascular invasion.[14] Adjuvant radiation to the involved lymph node basin is suggested in the setting of extranodal extension or extensive involvement, that is, 4 lymph nodes.[15] The role of lymphadenectomy has not been adequately addressed in the literature.

The role of chemotherapy in metastatic disease is not clear, but sweat gland carcinomas are considered chemoresistant (Table). Several combinations have been used with short-term responses. In one case treated with doxorubicin, mitomycin, vincristine, and 5-FU followed by maintenance therapy, the patient achieved a complete response that lasted for 16 months.[16] In another report, the treatment response was 2 years with treatment consisted of anthracyclin, cyclophosphamide, vincristine, and bloemycin.[17] Other combinations used in the literature include carboplatin and paclitaxel, which led to prolonged remission.[14] Cisplatin and 5-FU, or cisplatin plus cetuximab have been reported but with discouraging results.[18] Results to taxanes showed conflicting results.[19,20]

Hormonal therapy can be effective in cases in which estrogen and progesterone receptors are expressed, which can range from 19%-30% of eccrine sweat gland carcinomas.[21,22] Two cases have reported complete regression of lymph nodes in patients with metastatic disease, and in 1 patient relief from pain caused by bone metastases with durable response of around 3 years.[23,24] a

Experience with targeted therapy is very limited. Sunitinib has been reported to have some activity in metastatic adnexal tumors as a second-line therapy in 2 patients, with disease control for 8 and 10 months respectively.[25] Trastuzumab has been reported as having activity in 1 patient with strong HER2 expression (IHC score of 3+, denoting HER2 positivity), with complete regression of metastatic tumor. Upon progression in the same patient, a combination of lapatinib and capecitabine also showed positive response.[26]

In conclusion, metastatic sweat gland tumors treatment has not been standardized because of a dearth of reports in the literatures. Its early identification and complete excision gives the best chance of a cure. Neither chemotherapy nor radiation therapy has been proven to be of clinical benefit in treating metastatic disease.

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