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CASE REPORT

Unusual presentation of metastatic sebaceous carcinoma and its response to chemotherapy: is genotyping a right answer for guiding chemotherapy in rare tumours?

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ABSTRACT

Sebaceous carcinoma is a rare malignant tumour of skin. It commonly occurs in the head and neck region. The standard of care for localized disease is wide local excision followed by radiotherapy. Occasionally, sebaceous carcinoma can be associated with Muir–Torre syndrome, which is characterized by sebaceous lesions and carcinomas in the visceral organs. Metastatic sebaceous carcinoma is even rarer, with very little evidence about the role of chemotherapy in the treatment of metastatic disease.

Here, we report a case of recurrent sebaceous carcinoma metastatic to the rectum (initially mimicking rectal cancer and Muir–Torre syndrome) in which the disease responded to multiple lines of chemotherapy. We also review the available literature on chemotherapy in this disease and discuss the role of tumour profiling and genotype-guided selection of chemotherapeutics in such rare tumours.

Key Words Metastatic sebaceous carcinoma, genotyping, tumour profiles, Muir–Torre syndrome

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INTRODUCTION

Sebaceous gland carcinoma is a rare malignant tumour of meibomian gland adnexal epithelium that constitutes fewer than 1% of cutaneous malignancies[1]. It can also occur as a periocular or extraocular variant, the former being more common. Presentation varies from a painless subcutaneous nodule to pedunculated lesions, irregular masses, or diffuse thickening of the skin[2]. It is not clear if the rate of distant metastasis and recurrence is more common in the periocular type of sebaceous carcinoma[3]. Wide excision with negative margins and selective use of radiotherapy is the treatment of choice in localized tumours[4]. Being rare, distant metastasis has little reported experience about the efficacy of chemotherapy in its treatment.

Here, we report a case of recurrent metastatic sebaceous carcinoma, with metastasis to the rectum initially mimicking Muir–Torre syndrome, and response of the disease to multiple lines of chemotherapy.

CASE DESCRIPTION

An 81-year-old woman presented in the oncology clinic with colorectal carcinoma. Six years before presentation, she had been diagnosed with sebaceous carcinoma of the right ocular surface and lower eyelid. At that time, she had been treated with topical mitomycin, followed by excision and cryotherapy. One year before her current presentation, the tumour recurred over the right upper eyelid.

The patient declined debulking surgery and underwent external-beam radiation (6000 cGy in 30 fractions, with *en face* 8 MeV electrons). Combined positron-emission tomography–computed tomography showed hypermetabolic right obturator nodes and a soft-tissue opacity close to the sigmoid colon compatible with malignancy. However, colonoscopy showed only hemorrhoids.

One month before our evaluation, the patient had complained of rectal bleeding and mucous discharge. A sigmoidoscopy showed a friable mass at the sigmoid–rectal junction, which on biopsy was initially reported

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as adenocarcinoma with focal squamous-cell features. Further evaluation with magnetic resonance imaging revealed a circumferential lobulated rectal mass located approximately 10 cm from the anal verge, extending for 5–6 cm, with a more proximal 6 cm area of thickening possibly representing two separate lesions. Innumerable mesorectal lymph nodes were identified, together with bulky metastatic pelvic side wall lymph nodes involving the rectovaginal space, and liver metastasis.

The patient was initially considered to have stage IV rectal carcinoma as part of Muir–Torre syndrome and was started on FOLFOX chemotherapy [oxaliplatin, 5-fluorouracil (5FU), and leucovorin]. On further pathology evaluation by immunohistochemical staining, the rectal biopsy was found to be positive for Cam 5.2, epithelial membrane antigen, and acidophilin, and negative for chromogranin, synaptophysin, and cytokeratin 20. In addition, immunohistochemical staining for two mismatch repair genes (*MSH2* and *MSH6*) showed protein expression ruling out the possibility of Muir–Torre syndrome. The diagnosis was then re-established as metastatic poorly differentiated sebaceous carcinoma.

The patient continued on the FOLFOX regimen for 5 months. She experienced symptomatic improvement after 3 cycles of chemotherapy, and repeat computed tomography imaging showed stable disease with a mild decrease in the size of the hepatic lesions. She developed disease progression after 5 months (9 cycles) of treatment.

The patient was subsequently started on single-agent paclitaxel, and her disease remained stable on computed tomography at her 5-month evaluation. Subsequently, she developed paclitaxel-induced peripheral neuropathy. A tumour specimen was then sent for molecular tumour profiling (Caris Life Sciences, Irving, TX, U.S.A.).

Per the tumour profile report, the agents with anticipated potential benefit included docetaxel, paclitaxel, 5FU, capecitabine, pemetrexed, irinotecan, topotecan, and gemcitabine. The agents associated with potential lack of benefit were cisplatin, oxaliplatin, doxorubicin, other hormonal treatment, and HER2 inhibitory agents. The molecular tests showed negativity for estrogen, progesterone, and androgen receptor; negativity for HER2; absent MGMT; positivity for PTEN; and wild-type *PIK3C, C-Kit, BRAF, KRAS,* and *NRAS.*

On progression, our patient was switched to gemcitabine treatment based on the tumour profiling result. She nevertheless continued to have symptomatic progression manifested by fatigue, failure to thrive, and partial bowel obstruction. Three months later, she was unable to continue treatment, and she started on home hospice care. She passed away shortly thereafter, 17 months after the diagnosis of metastatic disease.

DISCUSSION

We report this case of metastatic sebaceous carcinoma for its unusual metastatic pattern masquerading as colorectal carcinoma, its favourable response to multiple lines of chemotherapy, and the clinical verification of response correlating with a tumour genotyping report.

Metastatic sebaceous carcinoma is rare, and this case mimicked rectal cancer at the outset because of an intraluminal rectal lesion. Retrospectively, the lesion was present a year before presentation as a perirectal nodule on combined positron-emission tomography–computed tomography; that nodule most likely grew and invaded the rectum over time. Unlike the usual metastatic pattern of bone and lung involvement from squamous cell carcinomas of the head-and-neck region, a mesenteric implant in this patient invaded and penetrated the colon and rectum in at least two areas, indicating an infiltrative growth pattern.

In patients diagnosed with colorectal cancer and sebaceous carcinoma, it is important to consider Muir–Torre syndrome, which is a subclassification of hereditary non-polyposis colon cancer syndrome, characterized by germline defects in one of the four DNA mismatch repair genes—namely, *MLH1, MSH2, MSH6,* and *PMS2*[5]. Muir–Torre syndrome is characterized by sebaceous neoplasms such as sebaceous adenomas, sebaceous carcinomas and epitheliomas, and gastrointestinal malignancies. In two thirds of patients, colorectal carcinoma is the most common manifestation, frequently involving the right colon as in hereditary non-polyposis colon cancer[5].

Immunohistochemistry staining was key in rendering the correct diagnosis in the present case. The tumour was negative for cytokeratin 20, a marker of colorectal carcinoma; positivity for Cam 5.2 and epithelial membrane antigen established the metastatic sebaceous carcinoma[6]. The negative immunohistochemical testing for *MSH2* and *MSH6* ruled out Muir–Torre syndrome and hereditary non-polyposis colon cancer.

The available literature on treatment recommends wide surgical excision with tumour-free margins, followed by adjuvant radiotherapy[4]. No study has looked at the pattern of metastatic disease sites and the choice of chemotherapy. Most of the available knowledge is derived from case reports. The only large study on sebaceous cell carcinoma is an analysis based on the U.S. Surveillance, Epidemiology, and End Results database, which reported up to 30% cancer-attributable mortality[7]. We searched the PubMed and Wiley online databases and found very few case reports on the experience of chemotherapy in metastatic sebaceous carcinoma (summarized in Table I).

Cisplatin-based chemotherapy was reasonably used in maximum cases, given that it has been the drug of choice for all head-and-neck cancers. Similarly, 5FU and paclitaxel have frequently been combined with cisplatin or used as single agents for second-line treatment. Murthy *et al.*[9] reported complete response after 5FU and carboplatin, enabling eyelid-sparing exenteration in a locally advanced sebaceous carcinoma. Joshi *et al.*[12] reported complete response in lung metastasis after paclitaxel and carboplatin chemotherapy. Our experience enhances the knowledge about chemotherapy in this disease. Our patient experienced a clinically meaningful benefit, mostly stable disease to mild regression, after receiving 5FU and oxaliplatin in combination and later on after single-agent treatment with paclitaxel, but no response to gemcitabine (Table I).

The role of molecular or genetic profiling and its guidance in cancer treatment are rapidly evolving. In principle, genetic profiling aims to identify genetic changes that are "targetable and actionable" with available agents; an example is the efficacy of erlotinib in non-small-cell lung

TABLE I Systemic chemotherapy for the treatment of metastatic sebaceous carcinoma: case reports

Reference	Regimen	Response	
		Type	Duration (months)
Koyama *et al.,* 1994[8]	Vinblastine 5 mg/m^2 and cisplatin 80 mg/m^2 for 3 cycles; doxorubicin 50 mg/m^2 and cisplatin 75 mg/m^2 for 2 cycles	Shrinkage of metastatic lesions; survived for 7 months on chemotherapy	7
Murthy *et al.,* 2005[9]	Carboplatin and 5-fluorouracil for 3 cycles, followed by radiotherapy	Shrinkage of tumour, enabling eyelid-sparing exenteration surgery	26
Husain *et al.,* 2008[10]	Carboplatin–docetaxel–bevacizumab for 2 cycles, followed by carboplatin–docetaxel for 1 cycle	Shrinkage of lung mass to 30%, after which surgery could be planned; survived till 6 months after report on case	>6
Osada *et al.,* 2011[11]	5-Fluorouracil 800 mg/m^2 on days 1–5 and cisplatin 80 mg/m^2 on day 1 monthly	Recurrence- and metastasis-free at 20 months	>20
Joshi *et al.,* 2012[12]	Every-3-weeks paclitaxel 175 mg/m^2 and carboplatin AUC 5 for 6 cycles	Completely resolved without recurrence at 6 months	>6
Jung *et al.,* 2013[13]	5-Fluorouracil 750 mg/m^2 and cisplatin 75 mg/m^2 on days 1–5 (2 patients treated: one for 8 cycles; one for 3 cycles); trial of doxorubicin for 2 cycles in 1st case	Chemotherapy stopped after 15 months because of intolerance; regression of cutaneous lesions after 3 months	15
Orcurto *et al.,* 2014[14]	5-Fluorouracil 750 mg/m^2 daily for 4 days, cisplatin 100 mg/m^2 and docetaxel 75 mg/m^2 every 3 weeks for 4 cycles; capecitabine 1000 mg/m^2 daily days 1–10 every 21 days	Complete response at more than 20 months	>20
Present report	5-Fluorouracil–oxaliplatin–leucovorin (FOLFOX) for 5 months, followed by paclitaxel for 9 months, followed by gemcitabine for 2.5 months	On FOLFOX, stable disease by CT at 5 months, but progression on CT at 7 months; stable disease on paclitaxel, but didn't tolerate; gemcitabine had no effect on progression	17

AUC = area under the curve; CT = computed tomography.

cancer patients with *EGFR* mutations[15]. In a pioneering study by Von Hoff *et al.*[16] that set out to demonstrate the clinical relevance of molecular profiling, actionable targets were identified in 98% of patients, and 27% of the patients in the genotype-guided treatment arm demonstrated longer progression-free survival. Foundation Medicine[17] (Cambridge, MA, U.S.A.) offers a wider range of testing that detects genetic mutations in 236 cancer genes simultaneously. Their test delivers information on both actionable mutations and on non-actionable ("passenger") mutations that are not amenable to current chemotherapy. In a prospective study testing the influence of Foundation Medicine profiling, the results led to alteration of therapy in 28% of the participants with advanced solid tumours, but results for patient outcomes are still pending[17].

In our case, the molecular tests detected negativity for estrogen, progesterone, and androgen receptor; negativity for HER2; absent MGMT; positivity for PTEN; and wild-type *C-Kit*, *BRAF*, and *PIK3C*, erasing the possible efficacy of the drugs targeting those pathways. The tumour did show wild-type expression for *BRAF*, *KRAS*, and *NRAS*, and therefore inhibition of the epidermal growth factor receptor using agents such cetuximab or panitumumab could have been considered for a subsequent line of treatment. However, the patient deteriorated rapidly and did not have a chance to use that actionable information.

Comparing our choice of chemotherapy and the tumour profile result, 5FU and paclitaxel were the agents with potential benefit. Oxaliplatin was predicted to be ineffective because of positive *ERCC1* expression[18], but our patient responded favourably to a 5FU–oxaliplatin combination, and it is hard to dissect whether the response was from the 5FU, the oxaliplatin, or both. Notably, the relationship of *ERCC1* expression with response to cisplatin-based treatment is debatable, and testing for *ERCC1* is not yet the standard of care. The anticipated response to gemcitabine was based on the absence of *RRM1* expression, whose presence has been associated with gemcitabine resistance in preclinical studies[19]; however, data from clinical studies are lacking. At this point, it is safe to assume that, in these rare tumours, molecular profiling can be most helpful if the rare tumour is recognized and if actionable driver mutations (as shown in other tumour types) are detected. Information on tumour molecular profiling potentially has importance in guiding the treatment of rare tumours, but additional clinical verification and experience are required.

SUMMARY

Metastatic sebaceous carcinoma can have an infiltrative, invading growth pattern. Chemotherapy with 5FU, paclitaxel, and platinum can be beneficial in controlling the disease. Tumour profiling and genotype-based chemotherapy could be a promising direction for future studies in this rare disease, but further clinical verification is required.

CONFLICT OF INTEREST DISCLOSURES

We have read and understood *Current Oncology*'s policy on disclosing conflicts of interest, and we declare that we have none.

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