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Skin metastases from endometrial cancer treated with electrochemotherapy: case report and review of literature

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Summary

Background: Cutaneous relapse from endometrial cancer is a rare event, and often is part of a plurimetastatic disease with poor prognosis. Besides palliative chemotherapy, no consensus is present in literature about the specific treatment of skin metastases, in particular in order to improve symptoms. *Objectives:* In this paper the authors present a case of multi-metastatic endometrial cancer patient with also cutaneous metastasis, treated with palliative systemic therapy and electrochemotherapy. In particular the authors will describe the clinical, dermatoscopic, and pathological features of cutaneous metastases and their management. A literature review on cutaneous metastasis from endometrial cancer is also presented. *Materials and Methods:* A PubMed research was made using the terms "endometrial carcinoma", "skin", "cutaneous", "metastasis", and "spread". *Discussion:* The present case of unusual localization of skin metastases from endometrial cancer is the second described in the literature. The other known cases of cutaneous metastasis from endometrial cancer are summarized and reviewed. Electrochemotherapy can be proposed as an effective and safe loco-regional therapy for skin metastases, especially in case of multiple lesions. To the present authors' knowledge this is the first case of cutaneous metastases from endometrial cancer treated with electrochemotherapy.

Key words: Skin metastases; Endometrial cancer; Electrochemotherapy.

Introduction

Endometrial cancer is the most frequently diagnosed gynaecological malignancy of the female reproductive system [1]. The majority of women with endometrial carcinoma are diagnosed with early stage disease (70%) and only 8% present distant metastases in lung, liver or bone [2]. Cutaneous metastases may occur as the initial manifestation of internal malignancy or late in the course of the disease [3]. Indeed, endometrial carcinoma rarely metastasizes to the skin, with a reported prevalence of 0.8% [3] and only 34 cases reported in literature. In this report, the authors present a case of a 58-year-old woman with unusual localization of skin metastases from endometrioid carcinoma of the uterus. In particular they would describe the clinical, dermatoscopic, and pathological features of cutaneous metastases and their management. A review of the literature on this topic is also discussed.

Case Report

A 58-year-old woman, in menopause status since seven years, was admitted to the present hospital, complaining of vaginal bleeding. An operative hysteroscopy with biopsy was performed, which revealed a moderately differentiated endometrioid adenocarcinoma of the uterus. MRI and CT scan confirmed no evidence of extra-uterine spread. Total abdominal hysterectomy with bilateral salpingo-oophorectomy, and pelvic lymphadenectomy with peritoneal washing were performed in November 2012. Pathological examination revealed moderately differentiated endometrial adenocarcinoma, endometrioid type, with two-thirds of myometrial and endocervical stromal invasion. Adnexa, peritoneal washing, and lymph nodes were negative (FIGO Stage II). The patient underwent adjuvant brachytherapy. She was followed up by gynaecological exam every three months and with PET/TC every six months. The follow up was negative until November 2014, when a total body PET-TC showed multiple nodal metastasis (mediastinum, left and right axilla, subcarinal region, celiac-pancreatic region), bone relapses (dorsal and lumbar vertebrae, sternum, and right iliac crest). A palliative chemotherapy with carboplatin (AUC5) p1 q 21 plus paclitaxel 60 p1, 7, 14 q21 and bisphosphonate (zoledronic acid) was started. After three cycles of chemotherapy, the imaging revealed a stable disease. However at the clinical examination, the authors noted the presence of burning, painful, and bloody multiple (>10) nodules measuring from < one to two cm on the anterior and left thoracic region. The nodules did not cross the median line. Every lesion was firm, reddish and strained, well-circumscribed, and fixed to surrounding soft tissue on erythematous background. A consult to dermatologists of the present hospital was required. They executed dermoscopy on lesions, revealing yellowish-white hue structureless areas, surrounded by arborizing and "wreath-like" vessels, and any follic-

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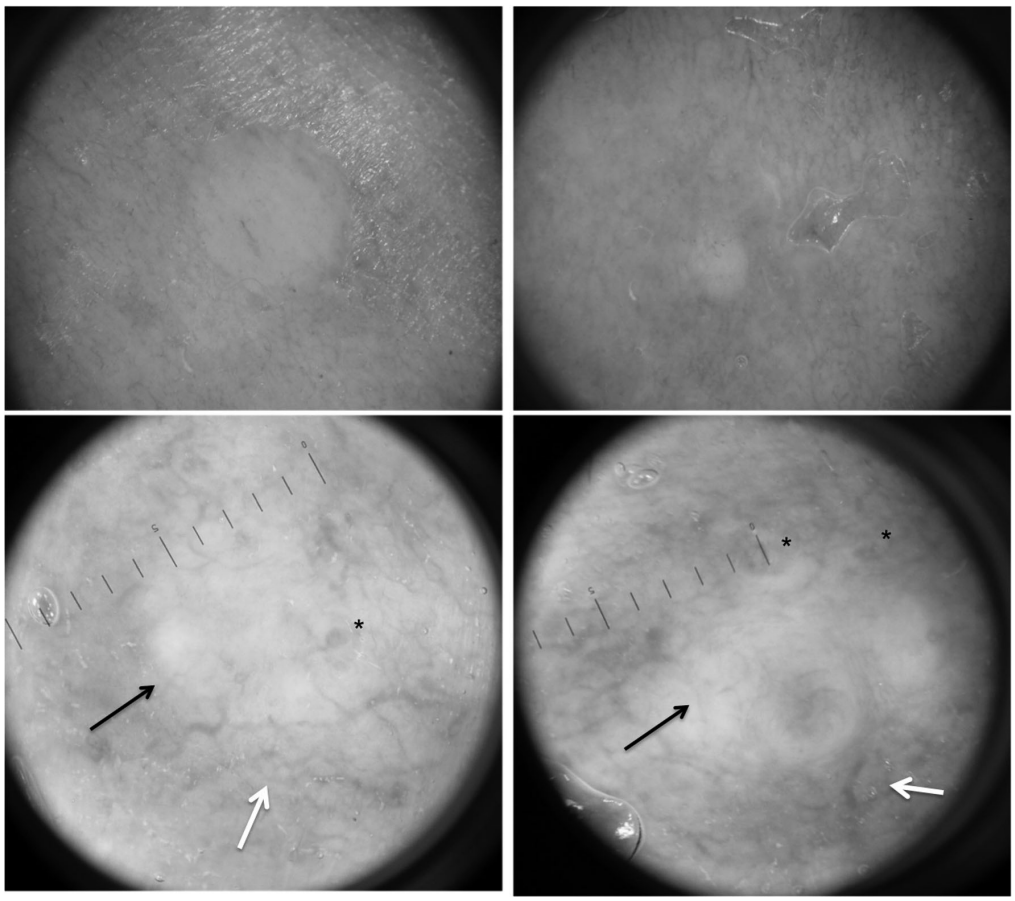

Figure 1. — Dermoscopy on lesions shows unspecific pattern, with yellowish-white hue structureless areas (black arrows), surrounded by arborizing and "wreath-like" vessels (white arrows) and follicular openings (asterisks).

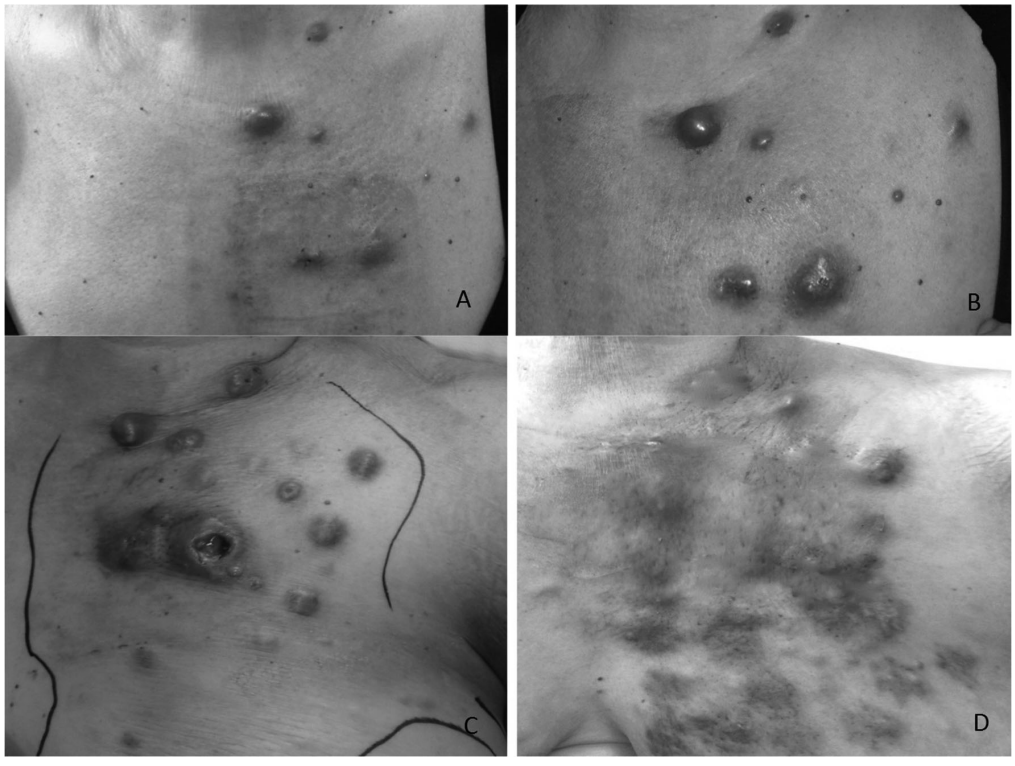

Figure 2. — A) Skin metastasis at first dermatological evaluation. B) After one month the number of lesions is increased. C) After about three months, cutaneous metastasis appear enlarged, ulcerated, and bleeding before the electrochemotherapy session. D) After about four months post-electrochemotherapy, hyperpigmented scarring, but also new lesions in untreated areas are observed.

ular openings (Figure 1). Punch biopsy of a nodule showed the presence of poorly-differentiated endometrioid adenocarcinoma in the skin, confirming the framework of thoracic cutaneous metastases. The patient was treated with electrochemotherapy, a technique for local control of cutaneous and subcutaneous metastases, in the attempt to stop bleeding, pain, and ulceration. According to the Standard Operating Procedures of Electrochemotherapy (ESOPE) guidelines [4], the present authors used bleomycin at dose of 15 mg/m^2 and a needle electrode–hexagonal array (length, 20 mm). An electric pulse generator and electrode were provided. Initially, erythema, slight edema, and then necrosis were observed at the treatment site accompanied by mild pain. After the authors obtained a partial recovery, with hyperpigmentation of the treated areas and the interruption of bleeding for each lesion (Figure 2). The patient was subjected to further systemic palliative chemotherapy but she died of disease in December 2015.

Discussion

Cutaneous metastases from a known primary malignancy ranges from 0.6% to 9%, usually appearing at two to three years after the initial diagnosis [5]. Clinically, skin metastases can take any form of lesions including nodules, papules, ulcers, and plaques, but the most common presentation is the nodule [5]. Few data exist on the dermoscopic features of cutaneous metastases, but the most common dermoscopic finding of non-pigmented lesions overall is a vascular pattern (linear irregular vessels, arborizing vessels, dotted, and comma-shaped vessels). Sometimes they can show a structureless or homogeneous pink appearance, without discrete vessels noted on dermoscopic evaluation [6]. Usually four histopathological forms involving the dermis; namely, nodular, infiltrative, diffuse, and intravascular [5-7]. However, clinical features of cutaneous metastases rarely provide information regarding the primary tumor, although the location of the tumor may be helpful because cutaneous metastases typically manifest in the same geographic region as the initial cancer. The most common cancers that present with skin metastases include breast (69%) followed by colorectal carcinoma (9%), lung carcinoma and melanoma (5%), and ovarian cancer (4%) [8]. Endometrial cancer rarely metastasizes to the skin with a reported prevalence of 0.8% [9]. Endometrial cancer usually relapses in the vaginal cuff, pelvic and para-aortic lymph nodes, peritoneum, lung, liver, and rarely in other sites such as muscle (2%) and spleen (1%) [10]. Several metastases routes are possible, depending on the histological type and local invasion. The patterns of spread include direct extension, lymphatic and haematogenous dissemination, and retrograde passage of neoplastic cells through the fallopian tubes [11, 12]. Endometrial skin metastases have been reported commonly at the site of initial surgery (laparotomy or laparoscopy) [13]. The mechanism is usually explained by hematogenous dissemination to the site of the recent trauma, seeding of neoplastic cells after direct contact between the tumour and the wound, surgical technique, and local immune response. A systematic literature research using the terms “endometrial carcinoma”, “skin”, “cutaneous”, “metastasis”, and “spread” identified only 34 cases of cutaneous metastasis from endometrial cancer [3,13-41] (Table 1). The total number of the found articles was 29 with 34 cases described. In total 56% (19/34) cases were endometrial adenocarcinoma, 6% (2/34) adenoepidermoid, 6% (2/34) papillary serous carcinoma, one case mixed mesodermal, one case carcinosarcoma, and nine cases were not specified. The mean age at diagnosis was 60. There were 17 women in Stage 1, three cases in Stage II, ten patients in advanced disease, and in three cases it was not reported. The most frequent sites of cutaneous metastases involved the scalp (5/34), the abdominal wall (6/34), the umbilical region (3/34), lower leg (2/34), while in other areas is less frequent. Only two articles reported the involvement of thorax and chest [15, 19]. The diameter of lesions ranges from 0.1 cm to 10 cm. The time interval between the primary diagnosis and the onset of skin metastases was a few weeks to about 35 months. There is no standard treatment for cutaneous metastases of endometrial cancer and it can be a challenging situation for the physician. Some authors include combined treatment with surgery, chemotherapy, radiotherapy, and hormone therapy. In patients with good clinical status, a combination of surgery and adjuvant therapy can improve survival, but in some cases only palliative care is feasible. Usually, cutaneous metastases are part of widespread disease, and despite the comprehensive treatments, the prognosis is poor. Mean life expectancy reported is between four to 12 months [38, 41]. Among factors influencing survivals, the interval time between diagnosis of endometrial cancer and the presence of skin metastases is important, but the percentage of survival is related mainly to the presence of multiple non-cutaneous metastases. Patients with only single skin metastasis, have a better survival rate compared to patients with multiple metastases (62% *vs*. 5%).

The present paper describes the case of a multi metastatic endometrial cancer patient, which also presents cutaneous metastases localized to left hemithorax without crossing the midline. Only another case has been described in the literature where skin metastases occurred 27 months after the primary surgery. The present patient was treated with palliative systemic therapy for the multiple visceral and bone metastases. Electrochemotherapy, a complementary therapeutic weapon for controlling cutaneous and subcutaneous metastasis, was successfully performed to reduce pain and bleeding. The presence of cutaneous and subcutaneous metastases had worsened patient’s quality of life, which complained about pain, ulceration, and bleeding. Their management is a challenge and depends on the number and size of the lesions, their anatomic location, and on the presence or absence of visceral metastases. In these patients the use of a multimodal treatment concept is advisable and along

Table 1. — *Clinical pathological characteristics of patients with endometrial cancer and skin metastases.*

Authors	Age	Primary treatment	FIGO Stage	Histology	G	N° of skin mts	Site	Other sites of metastases	Treatment skin metastases	Status (Survival in months)
Stonard et w al	73	Surgery, RT	IC	Endometrioid adenocarcinoma	-	1	Lower leg	-	-	-
Ma et al	60	Surgery +CT + RT	III C	Endometriod adenocarcinoma	-	1	Lower leg	Vaginal	CT + surgery	DOD (11 mo)
Damewood et al 1	57	Surgery+ RT	IB	Adenoepidermoid cancer	-	1	Left posterior calf	Lung	Excisional	-
Giardina et al	55	Surgery+ RT+CT	II C	Adenocarcinoma	G2	1	Subungual skin of the toe	Lung, left acetabular,	Amputation	DOD (few days)
Atallah et al	62	Surgery+ RT	I B	Endometrioid adenocarcinoma	G2	Diffuse disease	Vulvar	Pelvic tumor mass invading the bladder and rectum	Chemotherapy, uterine artery embolization	DOD (2 mo)
Chambo Filho et al	65	Palliative RT	IV	Endometrioid adenocarcinoma	G2	1	Clitoris nodule	Lung	Palliative care	DOD (6 mo)
Werchau et al	68	-	IB	Adenocarcinoma	-	3	Left breast lateral thorax left back	-	Palliative care	DOD
Ozsaran et al	60	Surgery+RT	-	Adenocarcinoma	G2	1	Umbilical region	Subcutaneous mass of abdominal wall	CT	DOD (12 mo)
Sengupta et al	62	Surgery + RT	IC	Adenocarcinoma	-	1	Umbilical region	no	Surgery + RT	ED after 14 mo
Luz et al	60	Surgery	IB	adenocarcinoma	G3	1	Umbilical region	no	Surgery + CT	Alive
Damewood et al 3	69	Surgery + RT	II	Adenocarcinoma	-	Multiple	Lower Anterior abdominal wall	Lung	-	-
Gucer et al	62	Surgery	IB	Endometrioid adenocarcinoma	G2	1	Abdominal scar	Small bowel	Surgery + CT	DOD (24 mo)
Espinos et al	77	Surgery + RT	IC	Adenocarcinoma	G3	1	Lower third of laparotomy scar	Retroperitoneal mass	RT and Progesterone	DOD (4 mo)
Damewood et al 5	68	Surgery+ RT	IB	Adenocarcinoma	-	Multiple	Axilla, shoulder, chest, breast , abdominal wall, anterior thigh , inguinal areas	Lung	No treatment	DOD
Mustafa et al	45	Surgery	IA	endometrial adenocarcinoma with areas of adenoacanthoma	G2	1	Scalp and Cranial Bone	Lung, pelvic mass	Progesterone and surgery	DOD
Debois et al	50		I	Adenocarcinoma			Scalp	Trunk	No	DOD
Debois et al	56		IC	Adenocarcinoma	G3		Scalp	Knee	Radiation	DOD
Damewood et al 4	58	Surgery + RT	-	Mixed mesodermal tumor		Multiple	Scalp	-	CT	ED
Kushner et al	56	Surgery + RT	IC	Endometrioid adenocarcinoma	G1	1	Scalp Cistic lesion	Lesion of the right ninth rib, pleura	Excision + CT	DOD (3 mo)
Damewood et al	53	Surgery	IB	Adenoepidermoid cancer		2	Head	Sacrum and left clavicule	No treatment	DOD
Sezen et al	67	Surgery,+ RT	III	Endometrioid adenocarcinoma	G2	1	Nose	Lung, liver	RT + CT	ED
Champman et al	73	RT+ surgery	-	-	-	-	-	Vagina	CT+Progesterone	-
Curtis et al	50	Surgery + CT	IIIA	-	G1	-	-	lung	Surgery	DOD (4 mo)
Kotwall et al	65	Surgery	IIIA	-	G2	-	-	-	-	-
Khalil	58	Surgery + RT	IC	-	G2	-	-	-	Surgery and Progesterone	DOD (48 mo)
Macias et al	56	Surgery	IIIA	-	G2	-	-	-	Surgery + CT	DOD (7 mo)
Joshi et al	45	Surgery +CT + RT	II	-	G1	-	-	-	CT + RT	-
Spencer et al	73	Surgery + RT	I	-	G3	-	Lower half abdomen	Vagina	Progesterone	-
Mandrekas et al	58	Surgery + RT	IIIC	-	G2	-	Right bid toe	Lung	-	DOD (6 mo)
Baydar et al	58	Surgery + RT	IB	-	G2	-	Initial surgery site	Vagina	CT	DOD (2mo)
Kim et al	54	Surgery + CT	IIIB	Papillary serous carcinoma	G3	Multiple	Pubic wall and vulva	Peritoneal carcinomatosis, tibial bone	CT	DOD (5 mo)
Elit et al	65	Surgery + RT	III	Papillary serous carcinoma	-	Multiple	Lower abdominal wall	Peritoneal carcinomatosis	CT + RT	DOD (17 mo)
Clairwood et al	57	Surgery + CT + RT	III	Carcinosarcoma	.	Multiple	Face and trunk	Lung, liver and spleen, then brain	RT	DOD (3 mo)
Augustin et al	78	Surgery + CT + RT	IIIC	Adenocarcinoma	-	Multiple	Anterior abdominal wall	Bowel	.	-

Abbreviations: G: Tumor Grading; CT: Chemotherapy; RT: Radiotherapy; DOD: Dead Of Disease; ED: Evidence of Disease.

with systemic therapy, which should also have a loco-regional effect, other local treatment options may be considered [6, 7, 9, 10]. In patients with good clinical status, a combination of surgery and adjuvant therapy can improve survival, but in some cases only palliative care is feasible [10]. When surgery cannot be performed with the prospect of a reasonable functional outcome, other options must be considered.

Conclusion

In conclusion electrochemotherapy can be proposed as an effective and safe loco-regional therapy for skin metastases as alternative treatment modality to conventional therapies, especially in case of multiple lesions [42]. It has been proven to ameliorate the symptoms of loco-regional relapse and to improve patients' quality of life. To the present authors' knowledge, this is the first case of cutaneous metastases from endometrial cancer treated with electrochemotherapy.

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