

# Cutaneous Metastasis of Uterine Adenocarcinoma: A Case Report and Review of the Literature

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## GOAL

To understand cutaneous metastasis of cancer, particularly uterine adenocarcinoma, to better manage patients with the condition

## LEARNING OBJECTIVES

Upon completion of this activity, you will be able to:

1. Describe the clinical presentation and pathogenesis of cutaneous metastases from uterine cancer.
2. Recognize the histologic characteristics of cutaneous metastases.
3. Manage cutaneous metastases in patients with cancer.

## INTENDED AUDIENCE

This CME activity is designed for dermatologists and general practitioners.

CME Test and Instructions on page 40.

This article has been peer reviewed and approved by Ranon Ephraim Mann, MD, Assistant Professor, Department of Medicine (Dermatology), Albert Einstein College of Medicine. Review date: June 2009.

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*Cutaneous metastases from cancer are relatively uncommon in clinical practice but when present may herald the diagnosis of internal malignancy. The most common sources of primary cancer are the breasts, lungs, large bowel, oral cavity, kidneys, stomach, ovaries, and malignant melanoma. Despite the high incidence of uterine adenocarcinoma, cutaneous metastases are uncommon. The*

most common presentation of cutaneous metastases is rapidly developing nodules or tumors. The diagnosis of cutaneous metastatic carcinoma hinges on histopathologic evaluation of the involved skin. We discuss and review the diagnosis and management of cutaneous metastasis of uterine adenocarcinoma.

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### Case Report

A 75-year-old woman presented with numerous widespread asymptomatic nodules of 1 month's duration on the lower part of her abdomen (Figure 1). Her medical history was remarkable for surgical removal of uterine cancer 4 years prior followed by chemotherapy. There was no evidence of recurrence.

Physical examination revealed multiple, firm, 5- to 20-mm, erythematous nodules on the lower part of her abdomen. She also had a large overhanging pannus with firm woody edema. Some of the nodules were oozing and produced a foul odor.

Examination of a biopsy specimen taken from one of the nodules showed metastatic carcinoma consistent with uterine adenocarcinoma. The patient was started on chemotherapy and died shortly after from a pulmonary embolus.

### Comment

Invasive neoplasms of the pelvic organs account for approximately 15% of all cancers in females.<sup>1</sup> Uterine adenocarcinoma is the most common of these malignancies, specifically endometrial adenocarcinoma. The most common symptom in up to 90% of females is postmenopausal uterine bleeding. Most females recognize the need for prompt evaluation, though only 10% to 20% of females with postmenopausal uterine bleeding have a gynecologic malignancy. Because of this prompt evaluation, 70% to 75% of females are diagnosed with stage I disease.<sup>1</sup>

Ninety-seven percent of endometrial carcinomas are adenocarcinomas.<sup>2</sup> Other histologic subtypes include adenosquamous, clear cell, and papillary serous carcinomas, as well as uterine sarcoma. Stage IVB cancer is characterized by distant metastases. Cutaneous metastasis from endometrial carcinoma accounts for 0.8% of all cutaneous metastatic cancers found on autopsy.<sup>3</sup>

**Epidemiology**—Skin cancer is the most common of all human cancers. Various forms of skin cancer are diagnosed in more than 1 million individuals in the United States each year.<sup>4</sup> Subcutaneous metastases from primary skin cancers are unusual. The most common sources of primary cancer are the breasts, lungs, large bowel, oral cavity, kidneys, stomach, ovaries, and malignant melanoma.<sup>5</sup> Uterine



**Figure 1.** Numerous widespread asymptomatic nodules. Erythematous nodules are 5 to 20 mm in diameter.

cancer is the most common malignancy of the female pelvic organs in North America.<sup>6</sup> Despite this high incidence, cutaneous metastasis from uterine adenocarcinoma is uncommon.

**Clinical Presentation**—Uterine adenocarcinoma most commonly is seen in women (mean age, 60 years) who present with postmenopausal uterine bleeding. Tumors usually are stage I and typically metastasize to the lymph nodes, lungs, and liver.<sup>7</sup> Cutaneous metastases are rare and in most cases, as in our patient, develop after the initial diagnosis of the primary tumor. In a small percentage of patients, metastases may be discovered at the same time as or prior to the diagnosis of a primary tumor.<sup>5</sup>

Patients with cutaneous metastases may present with rapidly developing nodules or tumors.<sup>8</sup> Any rapidly developing or eruptive lesions should warrant careful consideration of the possibility of metastasis. The nodules often are nonpainful, round or oval, firm, mobile, and rubbery in texture, and usually are flesh colored, though they also may be brown or blue-black. They range in size from barely perceptible lesions to large tumors. Although nodules are asymptomatic in most instances, pain and tenderness may be noted.<sup>8</sup>

Most cutaneous metastases occur in a body region near the primary tumor. Cutaneous metastases from ovarian and uterine cancers often are seen on the lower abdomen, as in our patient; groin; or upper thigh.<sup>8</sup>

**Pathogenesis**—In general, a malignant tumor may spread via the following modes: (1) infiltrating surrounding tissue, (2) the lymphatics, (3) vascular invasion, or (4) implantation in serous cavities. Metastases arise as disconnected extensions of a primary tumor, which occurs when cancerous cells break away from a primary tumor and spread

elsewhere. Lymphatic and vascular routes are the most common pathways. Lymphatic spread is the most common pathway for the initial spread of endometrial adenocarcinoma.<sup>9</sup> Tumor cells can readily enter the lymphatics and extend through these channels by permeation or embolization to the lymph nodes. Permeation is the growth of a colony of tumor cells along the course of the lymphatic vessel.<sup>10</sup>

Controlled remodeling of the extracellular matrix is essential for growth, invasion, and metastasis of malignant tumors. Matrix metalloproteinases and tissue inhibitor of metalloproteinases play an important role at different steps of malignant tumor growth. Matrix metalloproteinases increase degradation of the extracellular matrix that facilitates cancer spread, while overexpression of tissue inhibitor of metalloproteinases by cancer cells or by the host reduces the invasive and metastatic capacity of tumor cells.<sup>11</sup>

*Differential Diagnosis*—Differential diagnosis of uterine cancer includes nonmetastatic and metastatic lesions. Nonmetastatic lesions include cellulitis, dermatofibroma,<sup>12</sup> herpes zoster,<sup>13</sup> and pyogenic granuloma<sup>14</sup> (Table 1). Primary cancers with cutaneous metastatic lesions include endometrial carcinoma, lung cancer, melanoma, colon cancer, prostate cancer, and breast cancer (Table 2). The immunohistochemical battery of cytokeratin (CK)–7, CK-20, S100, carcinoembryonic antigen, vimentin, human melanoma black–45 (HMB-45), estrogen receptors, and progesterone receptors is a helpful adjunct in narrowing the differential

diagnosis of the primary site of a large proportion of cutaneous metastases.<sup>5,15-19</sup>

*Histologic Findings*—A biopsy of the skin helps in confirming a diagnosis of a tumor. The pattern noted and the microscopic appearance often suggests the likely tissue of origin, as in our patient. Tumors may show characteristics of the primary malignancy or may have a more anaplastic appearance. For anaplastic tumors, immunohistochemical marker studies and ultrastructural examination may help delineate the tissue of origin (Table 2).<sup>5,15-19</sup>

Metastatic tumors usually are round discrete lobules in the dermis with a grenz zone and are not usually associated with the epidermis. Physical patterns vary among different carcinomas. Fibrosis and inflammation may be present and vascular involvement is rare.

Histologically, endometrial adenocarcinoma is characterized by cribriform glands (or glandular crowding)(Figure 2) with little, if any, stromal tissue between the glands. Nuclear atypia, variation in gland size, and increased mitoses are common in adenocarcinoma.

On histologic examination, well-differentiated tumors may be confused with complex hyperplasia with atypia. Likewise, poorly differentiated tumors might be histologically mistaken for sarcomas. Other histologic variants of endometrial carcinoma also exist, such as adenosquamous carcinoma, clear cell carcinoma, papillary serous carcinoma, and uterine sarcoma. These histologic variants comprise 3% to 6% of endometrial carcinomas.<sup>20</sup>

Table 1.

**Nonmetastatic Lesions**

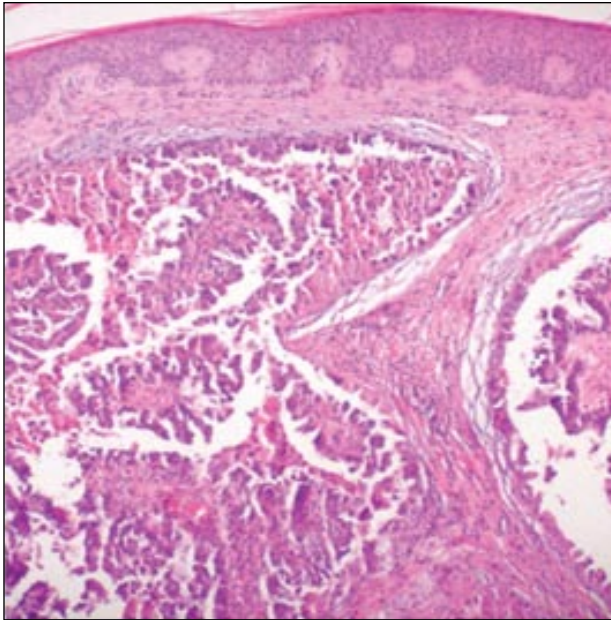
Disease	Clinical Features
Cellulitis	Acute infection of skin and soft tissues characterized by localized pain, swelling, tenderness, erythema, and warmth
Dermatofibroma	Common cutaneous nodule of unknown etiology Lesion frequently develops on the extremities and usually is asymptomatic
Herpes zoster	Painful grouped herpetiform vesicles on erythematous skin Vesicles initially are clear but eventually cloud, rupture, crust, and involute
Pyogenic granuloma	Bright red, friable, polypoid papule or nodule ranging from a few millimeters to several centimeters (average size, 6.5 mm) Bleeding, erosion, ulceration, and crusting frequently are noted

Table 2.

### Cutaneous Metastatic Lesions

Primary Cancers	Diagnostic Features of Cutaneous Metastases
Endometrial carcinoma <sup>5,15</sup>	<p>Endometrial cancers demonstrate substantial immunophenotypic diversity that remains apparent even within groups of similar histologic subtype and grade</p> <p>ERs, PRs, and p16 expression are more illustrative of tumor type and degree of differentiation than of endometrial origin</p> <p>The vimentin-positive/CEA-negative phenotype is the most constant among all endometrial cancers</p>
Lung cancer <sup>5</sup>	<p>History of primary lung cancer</p> <p>Lesions usually arise in the chest area</p> <p>Adenocarcinoma in the dermis is the most common form</p> <p>Diagnosis requires clinical correlation and immunohistochemical staining, including the application of antibodies for antithyroid transcription factor, CK-7<sup>+</sup>, and CK-20<sup>-</sup></p>
Melanoma <sup>16</sup>	<p>History of primary melanoma lesion</p> <p>Tumor cells are confined to the dermis, with a well-defined grenz zone and lymphovascular permeation</p> <p>Diagnosis is confirmed by HMB-45 positivity</p>
Colon cancer <sup>17</sup>	<p>History of colon cancer</p> <p>Lesions usually arise in the abdomen and groin areas</p> <p>Colon tumors with glandular features and the presence of goblet cells and intraglandular neutrophils are important clues suggestive of colonic origin</p> <p>Immunohistochemical staining for CK-7<sup>-</sup>/CK-20<sup>+</sup> markers confirms diagnosis</p>
Prostate cancer <sup>18</sup>	<p>Lower abdomen, genitalia, and thighs most often are involved</p> <p>Metastatic lesions usually are papules or nodules; may have a zosteriform distribution or mimic pyoderma</p> <p>Immunohistochemical staining for CK-7<sup>-</sup>/CK-20<sup>-</sup> and/or PSA<sup>+</sup> confirm diagnosis</p> <p>Increased levels of serum acid phosphatase and PSA also confirm diagnosis</p>
Breast cancer <sup>19</sup>	<p>Lesions are located mainly over the chest wall, though the face, neck, and upper and lower extremities also may be involved</p> <p>Nodular carcinoma, which is the most frequent clinical presentation, appears as cutaneous or subcutaneous, solitary or multiple, pink to reddish, firm, rarely ulcerated nodules</p> <p>Immunohistochemical evaluation for the presence of ERs, PRs, and CKs is helpful in confirming diagnosis</p>

Abbreviations: ER, estrogen receptor; PR, progesterone receptor; CEA, carcinoembryonic antigen; CK, cytokeratin; HMB, human melanoma black; PSA, prostate-specific antigen.



**Figure 2.** A biopsy specimen of the anterior abdominal wall metastatic lesion shows unaffected epithelium and subcutaneous glandular pattern of uterine adenocarcinoma (H&E, original magnification  $\times 20$ ).

**Medical Care**—In patients presenting with cutaneous metastases, appropriate workup and treatment of primary cancer should be immediately started. Palliative care is given for asymptomatic cutaneous metastatic lesions in patients with untreatable primary cancers. This care includes keeping lesions clean and dry as well as debridement if the lesions are bleeding or crusted. Hydrocolloid dressings may be used to help prevent secondary infection. Liquid nitrogen cryotherapy, photodynamic therapy, and conventional surgery also may be useful for palliation.<sup>21,22</sup>

Short-wavelength radiation therapy may be helpful to provide symptomatic relief for painful lesions using superficial electron beam therapy. Controlled temperature probe cryotherapy, CO<sub>2</sub> laser therapy, electrochemotherapy, and other treatment approaches also may be of value. Pulsed dye laser treatment may reduce blood flow to highly vascularized metastases. Intralesional chemotherapy and cytokine therapy can be useful, and topical retinoids or immunomodulators such as imiquimod offer promise in select cases.<sup>21-23</sup>

With improvements in surgical procedures and cure rates, the probable course of cancer for the majority of patients is now largely determined by metastasis rather than growth of the primary tumor itself. Thus, metastasis has received increased attention over the past decade. Several of the molecular events crucial for metastatic dissemination

have been identified and this information is now being used to design therapeutic strategies to inhibit metastasis formation. Even though the molecular events involved in the dissemination of malignant disease are only partially known, several promising agents are being tested for their capacity to limit the spread of cancer. A few clinical trials using ifosfamide, nonanticoagulant heparins, and clodronate are promising and have shown benefit in prolonging survival and disease-free state, particularly when the therapy is employed on an adjuvant basis.<sup>24-26</sup>

**Prognosis**—The mortality rate in patients with cutaneous metastases is high. The appearance of cutaneous metastases signals widespread metastatic disease, resulting in a poor prognosis. Patients often survive for a short period. Exciting advances in chemotherapy have greatly increased survival in recent years.<sup>27</sup>

## Conclusion

Invasive neoplasms of the pelvic organs account for approximately 15% of all cancers in females. Uterine adenocarcinoma is the most common of these malignancies, most frequently diagnosed as stage I disease. Stage IVB cancer is characterized by distant metastases. Cutaneous metastasis from endometrial adenocarcinoma is rare but should be considered in patients who present with rapidly developing asymptomatic nodules or tumors in the lower abdomen and/or groin area. Skin biopsy evaluation is needed to confirm the diagnosis. Palliative care including local lesion care, cryotherapy, photodynamic therapy, and short-wavelength radiation therapy may provide symptomatic relief. Cutaneous metastasis has a poor prognosis and is associated with a high mortality rate.

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