Case Presentation

Cutaneous metastasis of high-grade serous adenocarcinoma secondary to a gynecological malignancy

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Keywords: adenocarcinoma, cutaneous, dermatopathology, endometrial, fallopian, gynaecology, immunohistochemistry, oncology, ovarian

Dermatology Online Journal

Vol. 31, Issue 4, 2025

Abstract

Cutaneous metastases from malignancies of gynecological origin are rare but have been described over the vulvovaginal area in the setting of ovarian, endometrial, and fallopian tube neoplasia. We present an 89-year-old woman with multiple nontender, fleshy, skin-colored nodules with central ulceration and bleeding over the mons pubis. Skin biopsy and immunohistochemistry of these tumors were in keeping with metastatic high-grade serous adenocarcinoma secondary to a gynecological malignancy. This brief report aims to raise physician awareness about this rare skin presentation, which is unfortunately associated with a poor prognosis.

Introduction

An 89-year-old woman was referred by the gynecology team in view of multiple nontender, fleshy, skin-colored nodules with central ulceration and bleeding over the mons pubis. Their diameter ranged from 1cm to 3cm, on a background of a distended mass over the same area (Figure 1). These findings were suspicious for cutaneous malignancy. The skin lesions had been present for at least seven months and were associated with palpable nontender bilateral inguinal lymphadenopathy. There were no umbilical lesions. She was very frail and had multiple medical comorbidities including chronic heart failure, chronic kidney disease, diabetes mellitus, and myelodysplasia. She was completely dependent during activities of daily living.

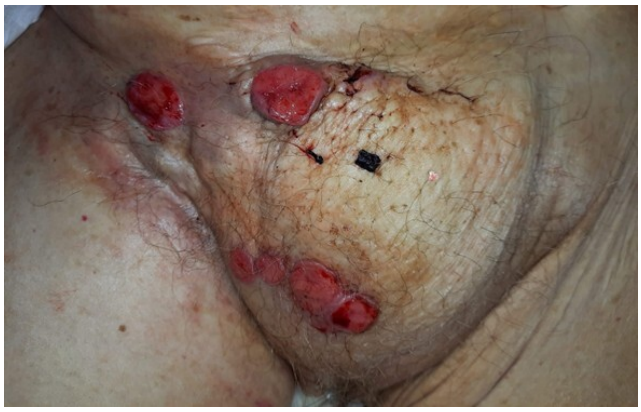

Figure 1. *The patient's mons pubis, showing multiple nontender, fleshy, skin-colored nodules with central ulceration and bleeding, their diameter varying from 1cm to 3cm, on a background of an underlying mass.*

Case Synopsis

The patient had already been seen by the gynecology team two years prior in view of postmenopausal bleeding. A transvaginal ultrasound done at the time had shown an endometrial thickness of 12.3mm, irregular vascular growths from the endometrium, and fluid in the endometrial cavity. Liquid based cytology from the cervix revealed atypical glandular cells of uncertain significance, favoring endometrial origin owing to the presence of endometrial cells. She was planned for urgent dilatation and curettage in view of this. However, the patient did not attend and was lost to follow-up.

A skin biopsy of the skin lesions showed extensive dermal infiltration by a markedly pleomorphic and briskly mitotic population of neoplastic cells variably organized in solid nests, angulated glands, and papillary configurations (Figure 2). Extensive ulceration of the overlying skin

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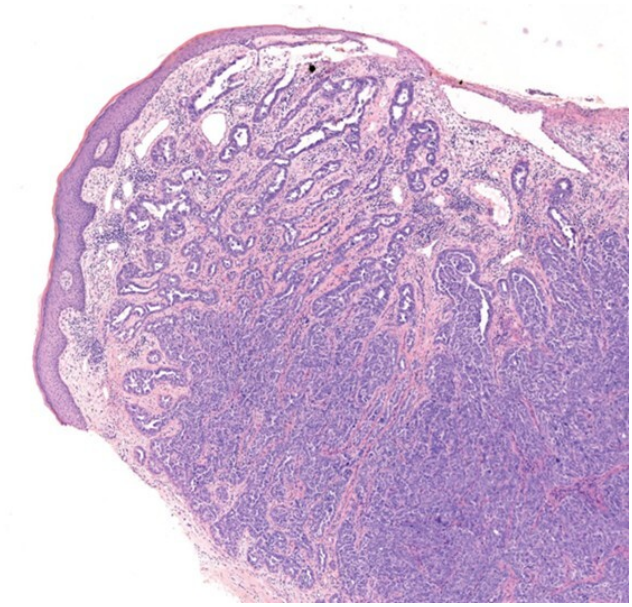

Figure 2. *Infiltration of the dermis by a high-grade adenocarcinoma comprised of glands, solid nests, and papillaroid configurations.*

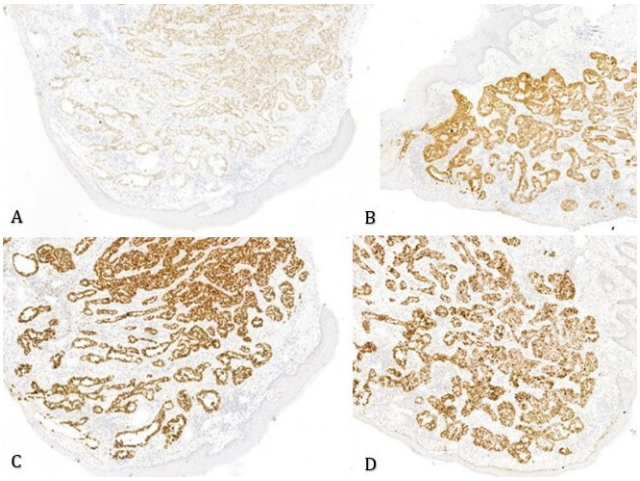

Figure 3. ***A-D)*** *Immunohistochemistry for paired box gene 8 shows nuclear positivity in the neoplastic glands, supporting the origin from a gynecological primary.*

was evident. Immunohistochemistry showed strong and diffuse expression of paired box gene 8 (Figure 3) and epithelial membrane antigen, supporting a gynecological primary. The tumor showed strong expression of both WT1 and p16 and a mutational p53 signature was also observed, with strong nuclear expression. There was no observed estrogen receptor expression. These findings were in keeping with metastatic high-grade serous adenocarcinoma.

Blood tests revealed an elevated CA-125 of 1278.2U/ml (range 0-30.2U/ml) and an elevated Ca19.9 of 386.9U/ml (range 0-31U/ml). A repeat transvaginal ultrasound was attempted by the gynecologists, but it was unsuccessful because of patient inability to cooperate. A computed tomography scan of thorax, abdomen, and pelvis reported an atrophic uterus with fluid retention in the endometrial cavity, a nodular irregular thickening of the skin in the groin especially the right side, and lymphadenopathy along abdominal aorta and external iliac arteries. She also had subscapular liver deposits and small bilateral pleural deposits with enhancing right axillary lymph nodes. These findings were consistent with liver and lung metastases, most likely gynecological in origin. Given her poor general state, it was deemed that the patient would not likely benefit from further gynecological investigations, surgery, or chemotherapy. Therefore, she was referred for palliative care and she sadly passed away within three months of diagnosis.

Discussion

Cutaneous metastases from malignancies of gynecological origin are rare but have been described in the setting of ovarian,[1] endometrial,[2] and fallopian tube[3] neoplasia. The reported frequency of cutaneous metastasis in ovarian carcinoma ranges from 1.9% to 5.1%, compared to 0.8% to 1.0% for endometrial carcinoma.[1,2] Fallopian tube carcinoma may present similarly to ovarian carcinoma both clinically and histologically, as well as in the way it metastasizes.[4] A study done by Otsuka and Matsuura reported that 5.8% of their patients with ovarian or fallopian tube cancer had skin metastasis.[3]

The most common site for ovarian, endometrial, and fallopian tube skin metastasis is the umbilicus, known as Sister Mary Joseph nodule (SMJN), which presents as papular and erythematous lesions in the umbilicus.[5] Other reported cutaneous sites for metastasis include the vulvovaginal area, chest, back, arm, thighs, and even nasal skin for ovarian carcinoma. For endometrial carcinoma, the vulvovaginal area, abdominal skin, previous surgical scars, scalp, and lower limbs are the most common metastatic sites.[1,6] The skin lesions may present as solitary or multiple nodules, carcinoma erysipeloides, and erythema.[1]

It is postulated that skin metastasis may occur through direct invasion from the underlying tumor, through extension of tumor cells via the lymphatic system and through seeding of tumor cells during surgical procedures.[1] In the case of SMJN, umbilical metastasis may occur through seeding tumor cells, which are carried off from the primary tumor site within the intraperitoneal cavity, through the peritoneal fluid. The weak anatomical depression of the umbilicus within the anterior abdominal wall helps the tumor cells to accumulate within this umbilical cul-de-sac.[7] Furthermore, lymphatic spread from retrograde lymph flow through the inguinal lymph nodes or the lymph nodes of the falciform ligaments, both of which pass through the umbilicus, may also play a role. SMJN formation via the hematogenous spread is very rare.[7]

In our case, histology and immunohistochemistry were those of high-grade serous carcinoma (HGSC). HGSC is the most common primary malignancy of the ovary and is thought to derive from the epithelium of

the fallopian tube. HGSC may also arise from the endometrial cavity, with this being most frequently seen in the setting of elderly patients in the context of endometrial atrophy. In this case, both the morphology of the tumor and strong expression of paired box gene 8 on immunohistochemical grounds supported a gynecological primary. A mutational pattern of p53 expression, which may range from strong and diffuse nuclear expression to absent expression (null phenotype) or cytoplasmic staining, is seen in virtually all serous carcinomas.[8] The presence of strong and diffuse WT1 staining is usually seen with tubo-ovarian primary tumors, with primary endometrial disease usually showing patchy or absent expression (although a subset of cases may show strong expression). Expression of p16 tends to be diffuse and intense as well in HGSC. HGSC may also show estrogen receptor positivity, although this was negative in our case.[8]

There is no standard treatment for cutaneous metastasis from gynecological malignancies but it may include surgery, chemotherapy, and/or radiotherapy. The therapy of choice depends on multiple factors, including the affected sites of metastasis, history of previous treatment and patient performance status.[9] The prognosis of skin metastasis from both ovarian and endometrial origin is very poor, with overall survival time from skin metastasis diagnosis being four months (range, two to 65 months) for ovarian malignancy[10] and four to 12 months for endometrial malignancy.[11]

Conclusion

Skin metastasis from gynecological malignancies is rare and carries a poor prognosis. Management should be multidisciplinary, including systemic and surgical treatment were possible, which may help improve survival times. Palliative management should also be incorporated to help with symptom control.[1,9]

Potential conflicts of interest

The authors declare no conflicts of interest.

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