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CASE REPORT

The Role of Palliative Radiation to Skin Metastases in a Patient with Endometrial Carcinoma and Known Lynch Syndrome: A Case Report

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Abstract

Lynch syndrome, or hereditary nonpolyposis colorectal cancer, is an autosomal dominant condition that predisposes individuals to many different types of cancer, including endometrial carcinoma. Because the risk of malignancy is high, several early surveillance measures are taken to ensure the early detection of cancers in patients with Lynch syndrome. This case describes a patient in her 50s who presented to the clinic with irregular menstrual bleeding, leading to an official diagnosis of biopsy-confirmed high-grade serous endometrial carcinoma, stage IIIC. Just before this diagnosis, the patient discovered that she had a family history of Lynch syndrome, prompting the patient to get tested. She was found to have a positive MSH2 mutation, consistent with Lynch syndrome. Despite neoadjuvant therapy, disease progression ultimately led to the development of painful skin metastasis, a rare form of metastatic spread. The patient and her treatment team elected to pursue palliative radiation for these lesions, successfully aiding in pain relief. This case emphasizes the importance of proper genetic counseling for patients with known Lynch syndrome, adhering to surveillance guidelines for Lynch syndrome, and recognizing skin metastases, as they can cause significant discomfort to the patient.

Keywords: Lynch syndrome; skin metastasis; endometrial carcinoma; palliative radiation; cutaneous metastasis

Abbreviations: SLN: sentinel lymph node; H&E stain: hematoxylin and eosin stain; IHC: immunohistochemistry; EBRT: external beam RT; TH: total hysterectomy; BSO: bilateral salpingo-oophorectomy; SBRT: stereotactic body radiation therapy; RT: radiation therapy; ER: estrogen receptor; PR: progesterone receptor

Introduction

Lynch syndrome, also known as hereditary nonpolyposis colorectal cancer, is a hereditary syndrome that predisposes affected individuals to a variety of cancer types.1 It is the most common cause of hereditary colon cancer, but it also increases the risk of endometrial, stomach, liver, kidney, ovarian, and brain cancer [1] Lynch syndrome occurs due to an autosomal dominant mutation of DNA mismatch repair genes (MLH1, MSH2, MSH6, PMS2). [1, 2] Given the elevated risk of malignancies, the CDC recommends early cancer screening for individuals affected by Lynch syndrome. The recommendations include a screening colonoscopy every 1-2 years starting at the age of 20-25, prophylatic hysterectomy and bilateral salpingo-oopherectomy at completion of childbearing, endometrial biopsy every 1-2 years, testing for H. pylori, upper endoscopy at time of colonoscopy every 2-4 years starting at age 30-40, skin exams every 1-2 years, CA-125 tests yearly, and annual urine analysis. [3]

Endometrial cancer is the most common gynecological cancer among women [4]. In contrast to cervical cancer which can be screened with a Pap smear or breast cancer which can be screened with a mammogram, there is no routine screening test for endometrial cancer. Risk factors for developing endometrial cancer in women are related to lifetime estrogen exposure, including increased age, obesity, early age at menarche, late menopause, and use of tamoxifen.5 Some studies suggest testing new diagnoses of endometrial cancer for DNA mismatch repair mutations, as 3% are caused by Lynch syndrome.5 To that end, those with Lynch syndrome have an estimated 60% lifetime risk of developing endometrial cancer [4].

The classic presentation of endometrial cancer is a postmenopausal woman who reports abnormal uterine bleeding [5, 6]. This presentation warrants further evaluation with endometrial biopsy and transvaginal ultrasound to solidify the diagnosis. In practice, ultrasound is used to evaluate for thickened endometrial tissue suggestive of malignancy; however, an endometrial biopsy is required to make the diagnosis [6]. Cancer staging involves biopsy and further imaging, and any noted metastasis leads to a diagnosis of stage IVB endometrial carcinoma according to the FIGO clinical staging scale [6].

According to the American Osteopathic College of Dermatology, cutaneous metastasis occurs when cancer cells from endogenous cancer spread to the skin through lymphatics, blood, or by direct spread through surgical scars [7]. Cutaneous metastases most commonly originate from the breast; however, metastases originating from the lung, colon, kidney, oral cavity, cervix, ovaries, and pancreas have also been reported.7 Skin findings are occasionally the presenting sign of an internal malignancy, and presentation often includes fast-growing, firm, mobile, painless pink lesions that may ulcerate.7 Biopsy should be performed to aid diagnosis and would ultimately reveal the underlying pathology of the primary malignancy.7 Cutaneous metastases are rare, and an endometrial etiology of skin metastasis has a reported incidence of only 0.8% [8].

Case

Evaluation and Diagnosis

A 52-year-old G5P5 perimenopausal Caucasian female presented to clinic in November 2022 with concern for irregular menstrual bleeding. History revealed that she had been having regular periods until May 2022. The patient underwent an annual wellness exam in July 2022, with normal cervical cytology on Pap smear, high-risk HPV negative. She was overall healthy and a non-smoker. Relevant family history includes a female paternal first cousin diagnosed with breast cancer in her early 40s and a different female maternal first cousin with an unknown cancer type who was later diagnosed with Lynch Syndrome in October 2022. This diagnosis prompted the present patient to undergo genetic testing. Shortly thereafter, the patient presented to her PCP in mid-to-late November 2022 for abnormal uterine bleeding. As is standard, the patient underwent a pelvic ultrasound, revealing a 6.1x4.5cm uterus with an endometrial stripe of 6.4mm. An endometrial biopsy confirmed a diagnosis of high-grade serous carcinoma. The patient was taken to the operating room in December 2022 for explorative laparotomy with intent to perform a total abdominal hysterectomy (TAH), bilateral salpingo-oophorectomy (BSO), and to obtain comprehensive surgical staging, but this was ultimately

aborted due to extensive non-resectable disease, including right pelvic sidewall involvement. Clinically, the patient was staged with IIIC unresectable high-grade serous endometrial cancer. Her genetic testing results confirmed a mutation in the MSH2 gene consistent with Lynch Syndrome in mid-December 2022.

Family History and Genetics (seen by genetic counselor)

Given the patient's family history, she elected to undergo genetic testing. The patient had no Ashkenazi Jewish ancestry, and she was aware that there was a family history of Lynch Syndrome. At some point in her young adulthood, she was told she was a "carrier" but did not think she was personally affected. She had one sister with Lynch Syndrome who was concurrently diagnosed with ovarian and uterine cancer at age 38, and ultimately died due to complications of chronic vascular disease. Additionally, the patient's older brother was diagnosed with Lynch syndrome based on genetic testing, though he is living and healthy. The patient underwent genetic testing of 40 genes, which revealed she had a mutation in MSH2 gene called c.1827 del (p.His610Thrfs825), which is a pathogenic mutation associated with Lynch syndrome and is known to cause and increase risk for certain types of cancer. No other mutations were identified.

Treatment

Given the unresectable nature of her tumor, it was decided to pursue neoadjuvant therapy. Carboplatinum and then carboplatin--paclitaxel were administered every 3 weeks for a total of 4 cycles. Subsequent CT C/A/P with IV contrast and PET scan both confirmed disease progression. In March 2023, and periodically thereafter, pelvic-directed radiation was utilized with tandem/ovoid HDR brachytherapy to provide an interstitial boost. In June 2023, the patient was noted to have widespread metastatic disease and required urgent thoracic radiation for left lung obstruction. Single-agent pembrolizumab was then given for 4 cycles with mixed results, as imaging studies revealed some shrinking tumors with no new tumors developing. At the same time, multiple areas of symptomatic, progressive, subcutaneous deposits with a risk of rupturing the skin were noted to be causing significant pain and discomfort for the patient; these lesions were consistent with skin metastasis. The left upper arm revealed two adjacent ~5cm masses that were fluctuant, non-mobile with purplish discoloration and significant distention of the overlying skin, causing pain and reducing range of motion. An ~6cm left vulvar mass was noted, causing the patient pain and discomfort with walking, sitting, and urination. A nodular right lateral gluteal mass and a left superomedial newly developing gluteal mass were also identified and reportedly caused pain when sitting down. Her abdomen revealed two areas causing the inability to lay prone due to pain: one on the umbilicus and the other immediately above the pain pump. Umbilical retraction and obvious gross tumor on the pain pump incision were noted. Her care team determined that the progression of the tumor would erode the skin, and if opened, the pump would need to be moved/removed, for which she would not be a good candidate given her present health status. This area prompted discussion regarding radiation, though this could also cause pump malfunction and/or the need for explantation of the pump. Therefore, the patient was referred to palliative radiation oncology to further discuss treatment options for her subcutaneous disease. After discussions of the risks and benefits, she ultimately elected to undergo palliative radiation to address the subcutaneous areas of disease. The goal was to help with pain, decrease tumor volume, and reduce the risk of tumor rupture as the patient awaited possible clinic trial enrollment. Collectively, in November 2023, she underwent radiation to the periumbilical region to target the mass in the area around the pain pump, but also the other areas of concern including: the left upper arm, the left and right buttocks, the left vulva, and the majority of the right lower quadrant (Table I). She tolerated treatment well, aside from some left arm swelling after treatment to this area consistent with post-radiation skin reaction or inflammation of the skin. At her follow-up, the patient reported a significant decrease in pain post-radiation therapy, with once-weekly pain pump checks. In alignment with the patient's wishes to continue aggressive care, she and her care team were avidly searching for clinical trials until December 2023, when the patient had a large pulmonary embolism, ultimately resulting in her death.

Table 1: Treatment Summary for Palliative Radiation to Subcutaneous Metastases

Treatment Site	L upper arm, L vulva, R glute, umbilicus, RLQ
Fraction Number	3/5
Dose	1200/2000

Discussion

Although uncommon, patients affected by endometrial carcinoma can experience cutaneous metastases, most often as a late manifestation of the disease [9]. Accurate identification of a skin metastasis is essential in order to effectively treat the patient. The identification of a cutaneous metastasis can be done using a variety of methods with one approach being to: verify the locations of previously identified primary tumors, examine bodily areas paying close attention to sites near the primary tumor, palpate for nodules or underlying skin irregularities, examine the skin for signs of discoloration or ulceration, obtain a biopsy in order to perform a focused histopathological assessment.

A majority of cutaneous metastases occur in bodily regions in proximity to a primary tumor. In patients with endometrial carcinoma being identified as the primary tumor, common sites of metastases include the lower abdomen, the groin, and the upper thigh [10]. Other reported sites of metastases include the scalp, and acral locations such as the nose and the toe. Upon physical examination, solitary or multiple subcutaneous nodules may be palpated in the skin. These nodules may also present as pruritic [9]. In some cases, a zosteriform pattern may present on the abdominal wall [11]. Upon histopathological examination, most endometrial carcinoma cutaneous metastases present as adenocarcinomas with features resembling that of the primary tumor. With this presentation, histology will demonstrate invasive cells within the dermal layer, arranged in a glandular configuration [10].

The initial step in developing a treatment plan is to determine the origin of the tumor. Properly identifying whether a cutaneous lesion is of primary origin or of metastatic origin can alter the approach to patient care. Staging as well as sentinel lymph node (SLN) Mapping and Ultrastaging are key factors in accomplishing a focused treatment plan. SLN mapping is a validated technique for identifying potential lymph node metastases for patients who are at high risk [12]. This technique involves the injection of dye into the cervix. The dye will then be delivered to lymphatic channels such as the superficial subserosa, intermediate stromal, and deep submucosal lymphatic origin sites [13]. SLN Ultrastaging involves the examination of many hematoxylin and eosin (H&E)—stained slides with or without additional cytokeratin immunohistochemistry (IHC) staining. SLN Ultrastaging allows for the improved accuracy of detecting and locating micrometastases [12].

A variety of therapeutic options exist for treating a primary endometrial carcinoma itself, but treatment options diminish depending on whether the cancer extends to the extrauterine environment or involves distant metastases. Two general treatment approaches include chemotherapy and hormonal therapy. For extrauterine endometrial carcinoma with visceral metastasis, the recommended treatment plan includes systemic therapy with or without external beam radiation therapy (EBRT), total hysterectomy/bilateral salpingo-oophorectomy (TH/BSO), and stereotactic body radiation therapy (SBRT). For patients with local recurrent metastases such as to the vagina or pelvis, the second line treatment is radiation therapy (RT) with or without surgery/systemic therapy. For patients with distant metastases such as in our case, an aggressive "Therapy for Relapse" algorithm is typically followed. First, isolated metastases are resected via surgical intervention and EBRT or ablative therapy will be administered. Ablative RT can also be administered for up to 5 metastatic lesions only if the primary cancer has first been controlled. For patients with disseminated metastases, systemic therapy with or without palliative EBRT is recommended [12]. Combination chemotherapy with carboplatin/paclitaxel has been documented in the treatment of a case of endometrial cancer with cutaneous metastases. Treatment with carboplatin and paclitaxel in advanced or recurrent endometrial cancer has a response rate of 40% to 60% over the course of duration of 13 to 29 months. Hormonal therapy has not been shown to provide a survival benefit, but can be administered for palliative care [12, 14]. Possible hormonal therapeutic agents for metastatic disease include the following drugs in no par-

ticular order: megestrol acetate with alternative tamoxifen, everolimus/letrozole combination, medroxyprogesterone acetate/tamoxifen (alternating), progestational agents, tamoxifen alone, fulvestan, and aroma taste inhibitors. Prior to the initiation of hormonal therapy, patients should be screened for the expression of estrogen receptor (ER) or progesterone receptor (PR) in order to determine if a hormonal treatment approach is appropriate [12].

The case of this young female patient naturally draws attention to the necessity of standardized genetic screening recommendations for patients with a strong family history of Lynch syndrome, allowing patients with a positive mutation the opportunity to learn about the malignancy surveillance recommendations for this condition. Genetic testing is recommended for any patient with a first-degree relative diagnosed with Lynch syndrome or a close family history of cancers associated with Lynch syndrome, especially before the age of 50 [15]. Additionally, individuals with a personal history of multiple primary cancers, endometrial cancer before age 50, or colorectal cancer should be screened [16]. It is important to pair genetic testing with genetic counseling, as counseling helps individuals learn about the condition, understand the results, and navigate psychosocial and emotional implications before and after testing [17]. Children of patients with known Lynch syndrome ultimately have a 50% chance of inheriting the same mutation. Genetic testing revealed that two of this patient's five children were found to have MSH2 mutations.

As previously mentioned, the CDC has many surveillance guidelines and recommends endometrial biopsy every 1-2 years for patients with known Lynch syndrome, as well as a prophylactic hysterectomy and bilateral salpingectomy at the completion of childbearing [3]. These recommendations are in place due to the high risk of endometrial carcinoma, as seen in this patient. Had the patient known earlier that she was more than a carrier of the mutation, her case could have been prevented.

Conclusion

This case presents a young Caucasian female with a strong family history of Lynch Syndrome. This case serves as an important reminder to properly educate patients with strong family histories of genetic mutations on what these genetic mutations mean, and what screening tools are recommended for early detection of complications caused by the disease. In this case, the patient did not fully understand what it meant to be a "carrier" for Lynch Syndrome and hence did not undergo recommended screening and preventative measures. It was only upon the initial manifestation of her symptoms in her 50s that the patient began to understand the implication of being a "carrier" of an autosomal dominant disease.

Moreover, this case alludes to another important discussion, which is the role of palliative medicine within the realm of dermatology. Though not a primary dermatologic condition, the patient in this case experienced significant pain due to the rapid growth of her cutaneous metastases. The literature surrounding palliative care in dermatology is limited, likely because many dermatologic conditions are not immediately life-threatening. However, early initiation of palliative care may improve outcomes for patients with severe dermatologic conditions [18].

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