Case Report

Clear Cell Carcinoma of the Endometrium in a Patient Presenting with Postmenopausal Bleeding but Negative Endometrial Biopsy

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Keywords

Clear cell carcinoma · Endometrium · Postmenopausal bleeding · Cancer

Abstract

Endometrial carcinoma is the most common gynecological malignancy in the USA with approximately 66,570 cases and 12,940 deaths in 2020. Clear cell carcinoma (CCC) of the endometrium is an estrogen-independent type II endometrial cancer which accounts for <5% of endometrial cancer. When diagnosed roughly, 45% of patients have extrauterine metastases. Current American College of Obstetrics and Gynecology guidelines recommend transvaginal ultrasound for postmenopausal bleeding and a biopsy for those with endometrial thickness >5 mm. However, we present a case of a postmenopausal woman with a history of fibroid where endometrial biopsy has failed to make diagnosis twice. Hence, further testing should be performed in patients with unexplained postmenopausal bleeding including vaginal hysterectomy with lymph node dissection.

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Introduction

Clear cell carcinoma (CCC) of the endometrium is an estrogen-independent type II endometrial cancer [1]. It accounts for <5% of endometrial cancer. It was first described in 1967, and it was assumed to be derived from the Mullerian duct. However, its causes, pathogenesis, and risk factors have not been clearly identified. The most common presenting symptoms include vaginal discharge or vaginal bleeding, lasting for protracted periods including several weeks to years. Microscopically, CCC is described as clear hobnail cells that appear clear because of glycogen [2]. Biologically, CCCs have an increased propensity for lymphovascular invasion and intraperitoneal spread [3]. It is estimated that roughly 45% on initial presentation of CCC have extrauterine metastases. Overall 5-year survival is 42–62% in advanced stage compared to 68.8% when combining regionally advanced all uterine carcinoma [3]. Hence, it is essential to have better understanding of this disease entity for early diagnosis and treatment.

Case Presentation

This case reports a 67-year-old female, gravida 4, para 3, abortus 1 with a past medical history of hypothyroidism with goiter status after thyroidectomy, fibroid, hypertension, arthritis, factor XII deficiency, hyperlipidemia, prediabetes, and obesity. She presented with a chief complaint of postmenopausal bleeding of 5- to 6-year duration that has been worsening over the last few months with noticeable blood clots. Initially, there was mild occasional spotting for which she had transvaginal ultrasound (TVUS) done which showed endometrial hyperplasia and multiple fibroids. Endometrial biopsy done was negative for malignancy. On physical examination, the uterus was noted to be significantly enlarged to 12 week in size and globular.

Our patient continued to have bleeding and hence she underwent TVUS again which showed increased thickening of the endometrial stripe from 2.4 cm to 2.6 cm and 2 fibroids. The dimensions of the fibroids were noted to be similar from previous imaging, and there were no abnormalities in the ovaries. Due to the increase in endometrial stripe, the patient underwent an endometrial biopsy. Biopsy was once again negative for atypia or malignancy, but the result was limited due to scant sample obtained. Since the diagnosis was inconclusive and the patient continued to have postmenopausal bleeding, diagnostic hysteroscopy with dilatation curettage was planned. A specimen from endometrial curettage showed endometrioid adenocarcinoma.

The patient underwent a vaginal hysterectomy with bilateral salpingo-oophorectomy and lymph node dissection for endometrioid adenocarcinoma. However, surgical specimen biopsy showed CCC, with 44% myometrium involvement and cervical involvement. She was in FIGO grade 2 with notable myometrial invasion. Furthermore, adenomyosis and leiomyomas were also noted histologically. Fallopian tubes, ovaries, and pelvic and para-aortic lymph node showed no involvement of cancer.

She recovered well from surgery, and currently she is undergoing vaginal brachytherapy. She will be followed up with history and physical exam every 3 months for the first year, followed by every 4 months for the next year, followed by every 6 months for the next 5 years and then annually for cancer surveillance. In between this, she will also get CT scan of her abdomen and pelvis every 6 months for 2 years and then yearly for the next 5 years for screening. This is as per the National Comprehensive Cancer Network (NCCN) guidelines.

Discussion

Endometrial carcinoma is the most common gynecological malignancy in the USA with approximately 66,570 cases and 12,940 deaths in 2020. The mean age at the time of diagnosis is 63 years [4]. Morphologically, it is classified into 2 main types, type I and type II. Type I endometrial cancer is estrogen dependent and encompasses approximately 80–85% of the cases. Type II is estrogen independent and consists of serous carcinoma, CCC, and carcinosarcoma [1]. Uterine serous carcinoma has the worst prognosis followed by CCC of the endometrium [5].

Unlike the estrogen-sensitive endometrial adenocarcinoma, the risk factors for CCC have not been validated. Some studies have shown higher incidence of CCC with age, obesity, hyperinsulinemia, African American race, and in nulliparous women [6, 7]. Our patient was African American, morbidly obese (BMI 38.8), nonsmoker, multiparous, history of fibroid and Hageman factor deficiency (factor XII), and had a positive family history of uterine malignancy in her sister. Newer studies have also shown that CCC is associated with mutation of p53, p16, HER-2/neu overexpression, and decreased heterozygosity [8]. However, genetic testing was not done in our patient.

All uterine cancers including CCC are common in postmenopausal women, and they usually present with postmenopausal bleeding [3]. The American college of Obstetricians and Gynecologists (ACOG) recommends TVUS for women with postmenopausal bleeding and a biopsy for endometrial thickness >5 mm to rule out endometrial cancer [9]. However, only about 25% of the patients with postmenopausal bleeding and endometrial thickening >5 mm actually have endometrial cancer [10]. Our patient had negative biopsy twice, and hence it is very likely to think about benign causes of postmenopausal bleeding such as fibroid causing endometrial thickening and postmenopausal bleeding. Dilation and curettage were performed because of doubt of scant sample and showed less aggressive endometrioid adenocarcinoma rather than CCC. It was only the surgical specimen from the total vaginal hysterectomy with bilateral salpingo-oophorectomy which proved it to be CCC of the endometrium with cervix and myometrium involvement. Routine Pap smear was also not helpful for surveillance in our patient despite involvement of the cervix. By the time her outpatient workup for postmenopausal bleeding and surgery was completed, 6 months had passed by, and she already had advanced disease with International Federation of Gynecology and Obstetrics (FIGO) stage II.

The current NCCN guideline considers CCC as high-risk endometrial cancer and recommends total hysterectomy with bilateral salpingo-oophorectomy with maximum debulking surgery and surgical staging for CCC [11]. Surgical staging is done based on the FIGO staging [12]. Once staging is established, treatment modalities include systemic therapy with or without vaginal brachytherapy and external beam radiation. Hormonal therapy is not recommended for CCC. The detailed treatment is based on the staging and extent of disease and is shown in Figure 1. Studies have shown that stage I–II without lymph node involvement may be treated with radiation alone [3]. Our patient was in FIGO stage II with cervical and 44% myometrium involvement, and hence she was considered for vaginal brachytherapy alone without periodic follow-up.

Conclusion

In this case, we demonstrate that biopsy failed to establish a diagnosis due to poor sampling. Although fibroid was thought to be the likely cause of bleeding in our patient, further testing such as dilation and curettage should be performed in high-risk patients with unexplained postmenopausal bleeding.

Fig. 1. Treatment of CCC based on FIGO staging. CCC, clear cell carcinoma.

Statement of Ethics

This study protocol was reviewed and approved by the Institutional Review Board (IRB) of St. Joseph Mercy Oakland Hospital and has approved this case for publication. Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

Conflict of Interest Statement

The authors declare that there are no conflicts of interest regarding the publication of this article.

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Author Contributions

Swechchha Silwal wrote the first draft of the manuscript. Benedict Amalraj and Mohamed Mandeel helped with manuscript writing. Sumeet Kumar Yadav conceived the case and reviewed the manuscript. Geetha Krishnamoorthy contributed with final manuscript review and approval.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further enquiries can be directed to the corresponding author.

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