CLINICAL VIGNETTE

Post-menopausal Bleeding in a 64-Year-Old – Serous Carcinoma

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Case Report

A 64-year-old gravida 1 para 1 female with hypertension, untreated hyperlipidemia and Hashimoto's thyroiditis presents to primary care for abdominal bloating, mild urgency, and hematuria for 4 days. She denies fever. Point-of-care urinalysis shows trace blood and leukocytes and moderate ketones. She is started on Nitrofurantonin for empiric treatment of an uncomplicated urinary tract infection. The urine culture returns negative for bacterial growth and she re-presents to primary care 2 days later with ongoing symptoms despite antibiotic therapy. Pelvic exam reveals vaginal bleeding and an endometrial biopsy is performed. Biopsy reveals high grade malignant Mullerian neoplasm, compatible with high-grade serous carcinoma. Initial CT staging shows no intrathoracic metastatic disease. At the time of presentation, she was overdue for pap smear screening and had a suspicious breast lesion that was being followed by radiology.

Of note, her family history is negative for breast, ovarian and colon cancer. She is referred to gynecological oncology and underwent exploratory laparotomy, total abdominal hysterectomy, bilateral salpingo-oophorectomy, pelvic lymph node dissection, omentectomy and optimal tumor debulking. Surgical pathology of the omentum and sigmoid colon showed high grade carcinoma, stage IV disease. Tumor genetic testing showed p53 overexpressed, HER2 negative, focal loss of MLH1/PMS2. Methylation was present.

She underwent 6 cycles carbo/taxol/dostarlimab and maintenance dostarlimab. She returned to her primary care physician nine months after diagnosis and remained on maintenance dosrarlimab with minimal side effects besides neuropathy. Unfortunately, one month later she presented to the ER with abdominal pain and distention and was found to have hemoperitoneum, carcinomatosis and malignant ascites. She succumbed to her illness 11 months after initial presentation.

Discussion

Both prevalence and mortality from endometrial carcinoma have been increasing in the past decades.[1,2] Serous endometrial carcinoma is a particularly aggressive type of cancer that comprises 39% of all deaths from endometrial carcinoma, with only 10% of total cases.[3] The 2023 International Federation of Gynecology and Obstetrics staging system classifies any serous endometrial carcinoma as "aggressive", along with clear cell endometrial carcinoma, Grade 3 endometrioid carcinomas, gastrointestinal-type mucinous carcinomas and two other types of cancer.[4]

Similar to other endometrial cancer subtypes, serous carcinoma most commonly presents as abnormal uterine bleeding. However, the risk factors and patient demographics for serous carcinomas, as a type of non-endometrioid carcinomas, differ from endometrioid carcinomas, which are usually less aggressive and make up the majority of endometrial carcinomas. Patients with serous and clear cell carcinomas are older and more commonly parous rather than nulliparous. They also tend to have lower body-mass-index, although obesity is a risk factor for all endometrial carcinomas.[4–10]

Like all endometrial carcinomas, serous carcinomas are diagnosed and surgically staged. Serous carcinomas have complex papillary architectures and are thought to develop from hyperplasia with atypia. Cytology always has nuclear atypia. They can also be of mixed histology with endometrioid or sarcomatous cell types. Tumors with more than 10% serous component are classified as serous carcinoma with tumors with less than 90% serous component classified as mixed serous cancers.

Serous carcinomas tend to have a different molecular profile than the more common endometrioid tumors. While mutations in PTEN, microsatellite instability, and K-ras are common markers in endometrioid tumors, they are uncommon in serous carcinoma.[11] Ninety-three percent of serous carcinomas have p53 mutations, which is considered a late-stage marker and poor prognostic factor, with mutations in p16, e-cadherin, and HER2 amplification.[11,12]

The majority of patients presenting with serous carcinoma already have extrauterine spread.[13,14] The omentum is the most common intra-abdominal site for metastasis.[15] Even patients with tumors confined to the endometrium have 14% positive peritoneal cytology.[16] Chest radiograph is standard at the time of diagnosis to screen for lung metastasis. High-risk cancers such as serous carcinoma also have abdominal and pelvic imaging.

Like other endometrial carcinoma, the mainstay of treatment for serous endometrial carcinoma is surgery with hysterectomy and salpingo-oophorectomy, and commonly lymphadenectomy. Cytoreduction/debulking is often performed, as the strongest

predictor of survival is the amount of residual disease after surgery.[17–19] Surgery is often followed by adjunct chemotherapy, with carboplatin and paclitaxel showing optimal efficacy and low toxicity.[20] For stage III and IV endometrial carcinomas, dosarlimab is given in combination with carboplatin and paclitaxel and as a single drug maintenance regimen has shown increased survival.[21] For HER2 positive tumors, trastuzumab is often added.

Recurrence of endometrial cancers usually occurs within 3 years of treatment. The 5-year survival for serous carcinoma is around 55%, with poor prognostic factors including pure serous histology, p53 mutation and/or HER2 overexpression, later stage and depth of invasion during diagnosis, and older age.[3,22]

Timely investigation of abnormal uterine bleeding and associated diseases in patients with urinary tract infections are symptoms needed for early diagnosis and intervention. Initial screening for metastasis at time of endometrial carcinoma diagnosis and regular, subsequent surveillance is important. Unfortunately, our patient had several clinicopathological risk factors for the development, progression and ultimately mortality from endometrial carcinoma. These included older age, p53 mutation, an aggressive serous histological subtype, and late stage of disease at time of diagnosis. Even with a positive response to initial treatment and maintenance, she had rapid progression and metastasis of serous carcinoma.

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