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Concomitant Endometrioid Endometrial Carcinoma and Adult-Type Granulosa Cell Tumor in an Elderly Patient with Mismatch Repair Deficiency: A Case Report

Mismatch Repair Yetmezliği Olan Yaşlı Bir Hastada Eş Zamanlı Endometrioid Endometriyal Karsinom ve Erişkin Tip Granüloza Hücreli Tümör: Bir Olgu Sunumu

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Abstract: We present the case of an 82-year-old woman who was admitted with postmenopausal bleeding and was subsequently diagnosed with synchronous endometrioid endometrial carcinoma (FIGO grade 2) and adult-type granulosa cell tumor of the ovary. Histopathological and immunohistochemical analyses revealed mismatch repair (MMR) deficiency with loss of MLH1 and PMS2 expression. The coexistence of these two tumor types in a single patient, particularly in the context of MMR deficiency, is extremely rare. The case is discussed in light of current literature with consideration of its relevance to Lynch syndrome and the implications for genetic counseling.
Keywords: Endometrial carcinoma, Granulosa cell tumor, MMR deficiency, Lynch syndrome, Synchronous tumors, Postmenopausal bleeding

Özet: Bu çalışmada, postmenopozal kanama şikâyetiyle başvuran ve sonrasında endometrioid endometriyal karsinom (FIGO grade 2) ile overin erişkin tip granüloza hücreli tümörünün senkron tanısı konulan 82 yaşındaki bir kadın hastanın olgusu sunulmaktadır. Histopatolojik ve immünohistokimyasal incelemeler, MLH1 ve PMS2 ekspresyon kaybı ile karakterize MMR protein ekspresyon kaybı saptamıştır. Bu iki tümör tipinin aynı hastada birlikte görülmesi, özellikle MMR yetmezliği bağlamında, oldukça nadirdir. Olgu, mevcut literatür ışığında Lynch sendromu ile olası ilişkisi ve genetik danışmanlık gerekliliği açısından tartışılmıştır.
Anahtar Kelimeler: Endometriyal karsinom, Granüloza hücreli tümör, MMR yetmezliği, Lynch sendromu, Senkron tümörler, Postmenopozal kanama

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1. Introduction

Endometrial cancer is one of the most common gynecologic malignancies, particularly affecting postmenopausal women (1). It often presents with abnormal uterine bleeding and is typically diagnosed at an early stage, allowing for favorable prognosis. The pathogenesis of endometrial carcinoma involves a complex interplay of hormonal influences, environmental factors, and genetic alterations. Among these, deficiencies in the DNA mismatch repair (MMR) system have emerged as significant contributors, especially in the context of microsatellite instability (MSI) and hereditary cancer syndromes such as Lynch syndrome (2). Loss of expression of key MMR proteins—such as MLH1, PMS2, MSH2, and MSH6—can result in genomic instability and increased susceptibility to various malignancies, including those of the endometrium and colon (2).

Adult-type granulosa cell tumor (AGCT) of the ovary is a rare estrogen-secreting neoplasm that accounts for approximately 2–5% of all ovarian tumors (3). Originating from the sex cord-stromal tissues, AGCTs are often hormonally active and may lead to endometrial hyperplasia or even carcinoma due to prolonged estrogen stimulation (3). However, the synchronous occurrence of AGCT and endometrioid endometrial carcinoma is exceedingly rare, with only a limited number of cases documented in the literature. The simultaneous presence of these two tumor types in a single patient raises important questions about shared etiopathogenic mechanisms, hormonal influence, and potential genetic predispositions.

In this case report, we describe an 82-year-old woman who presented with postmenopausal bleeding and was found to have synchronous FIGO grade 2 endometrioid endometrial carcinoma and adult-type granulosa cell tumor of the ovary. Immunohistochemical analysis revealed MMR deficiency with loss of MLH1 and PMS2 expression. This rare co-occurrence, particularly in the context of MMR deficiency, underscores the need for comprehensive diagnostic evaluation, including molecular profiling and consideration of hereditary cancer syndromes (2). The case is discussed with reference to the current literature, highlighting the clinical, pathological, and genetic implications.

2. Case Report

An 82-year-old woman, gravida 5, parity 5, presented with postmenopausal bleeding. She had a BMI of 40 kg/m² and comorbidities including hypertension and chronic neuropathic pain. A family history was notable for breast cancer in a sibling. Transvaginal ultrasound revealed a 6 x 3.5 cm hyperechoic intrauterine mass extending to the cervix. Tumor markers were within normal ranges.

Histopathological analysis of the endometrial biopsy confirmed endometrioid adenocarcinoma, FIGO grade 3 with squamous differentiation. MRI showed deep myometrial invasion (>50%) with cervical stromal involvement. PET-CT revealed intense FDG uptake (SUVmax: 41) in the uterine mass. A right adnexal lesion with no significant FDG uptake was identified.

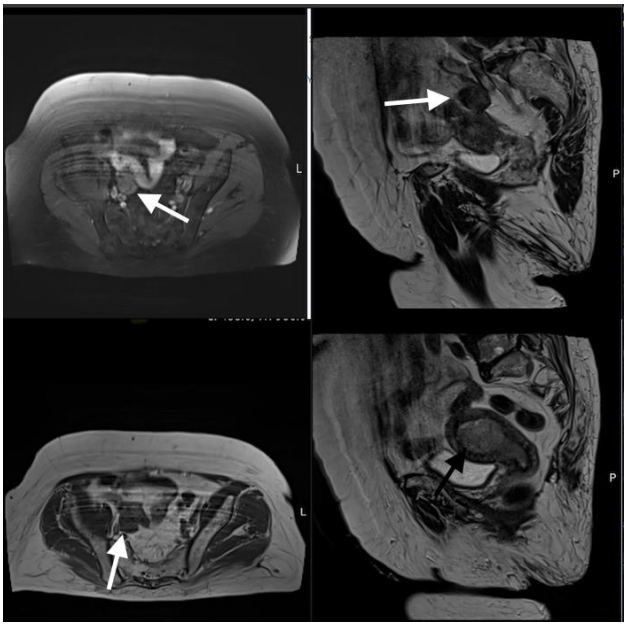

Figure 1. Axial and sagittal pelvic MRI image.The white arrows indicates a heterogeneous solid adnexal mass. The black arrow points to the irreguler endometrial thickening compatible with endometrial carcinoma

The patient underwent total abdominal hysterectomy, bilateral salpingo-oophorectomy, infracolic omentectomy, bilateral pelvic and para-aortic lymphadenectomy, and adhesiolysis.

Final pathology findings:

1. Endometrioid adenocarcinoma, FIGO grade 3, nuclear grade 2, 6 cm in diameter, with <50% myometrial invasion, no LVSI, and no cervical involvement.

2. Adult-type granulosa cell tumor (3.5 cm) in the right ovary; immunohistochemically positive for inhibin, calretinin, CD99, and SF-1; negative for WT1, Pan-CK, EMA, and ER.

Additional findings included adenomyosis, chronic cervicitis, follicular cysts, corpus albicans, and bilateral chronic salpingitis. Immunohistochemical staining demonstrated loss of MLH1 and PMS2 expression, indicating MMR deficiency. MLH1 promoter hypermethylation testing was not performed.

3. Discussion

Simultaneous presentation of endometrial carcinoma and adult-type granulosa cell tumor is rare. Estrogen produced by GCTs may contribute to endometrial hyperplasia and malignancy (4). However, in cases like this one, additional molecular alterations such as MMR deficiency may underlie tumor development.

MMR deficiency is commonly associated with Lynch syndrome and contributes to microsatellite instability in endometrial cancer (5,6). Loss of MLH1 and PMS2 may occur through germline mutations or somatic MLH1 promoter hypermethylation (7). These tumors are often characterized by prominent lymphocytic infiltration and may demonstrate favorable responses to immune checkpoint inhibitors (8).

While MMR alterations are well-described in endometrial cancer, they are rarely reported in granulosa cell tumors (9). Some studies have suggested the involvement of other genetic alterations, such as CHEK2 and PMS2 mutations, in GCT pathogenesis, though their clinical significance remains uncertain. This case emphasizes the importance of molecular characterization in patients with unusual tumor presentations and supports consideration of hereditary cancer syndromes when MMR deficiency is observed.

This case represents a rare co-occurrence of endometrioid endometrial carcinoma and adult-type granulosa cell tumor (GCT) in a postmenopausal woman with confirmed mismatch repair (MMR) deficiency, characterized by the loss of MLH1 and PMS2 expression. The synchronous presence of two histologically distinct tumor types - epithelial and sex cord-stromal - in a single patient raises important considerations regarding hormonal influences, shared oncogenic mechanisms, and the role of inherited genetic syndromes such as Lynch syndrome (5,6).

While endometrial carcinoma is commonly associated with MMR deficiency, the presence of such molecular alterations in granulosa cell tumors is extremely rare and poorly characterized (9). The identification of MMR deficiency in this patient underlines the importance of universal MMR testing in endometrial cancer, especially in older patients or those with a suggestive personal or family history. Although germline testing was not performed in this case, the possibility of Lynch syndrome necessitates referral for genetic counseling and consideration of further molecular workup (7).

From a therapeutic perspective, MMR-deficient tumors often exhibit increased sensitivity to immune checkpoint inhibitors, opening avenues for targeted treatment strategies beyond conventional therapies (8). Moreover, comprehensive surgical staging and histopathological evaluation remain essential in patients presenting with synchronous tumors to ensure accurate diagnosis and optimal management.

Clinicians should also be mindful that the coexistence of granulosa cell tumor and endometrial carcinoma, although rare, is a recognized association in the literature due to the estrogen-secreting nature of granulosa cell tumors. For this reason, in all cases where fertility-sparing surgery is considered, preoperative endometrial sampling is strongly recommended to exclude concurrent endometrial malignancy. When the uterus is not preserved, comprehensive staging surgery will typically identify any coexistent carcinoma; however, in uterus-preserving cases, omission of endometrial sampling may result in a missed diagnosis. Emphasizing this consideration is particularly important in surgical planning. In addition, incorporating mismatch repair (MMR) protein status assessment into the diagnostic work-up of such rare synchronous tumors may provide further valuable insights into tumor biology and guide management, as demonstrated in our case.

4. Conclusion

This case contributes to the limited literature documenting the coexistence of GCT and endometrial carcinoma in the setting of MMR deficiency. It highlights the diagnostic and

therapeutic complexities associated with such rare presentations and underscores the value of multidisciplinary care incorporating gynecologic oncology, pathology, molecular diagnostics, and genetic counseling for improved patient outcomes.

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