CASE STUDY

A Genetic Twist in Endometrial Cancer: Therapeutic Approach to a POLE Mutation Case.

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Keywords: Endometrial Cancer, POLE mutation, Gynecological Oncology, Radiotherapy

ABSTRACT

Background: Identifying POLE mutations in endometrial cancer has important therapeutic implications, as this molecular subtype often allows clinicians to safely avoid aggressive adjuvant treatments. Endometrial cancer is the most common gynecological malignancy in developed countries, predominantly of the endometrioid type. The Cancer Genome Atlas (TCGA) introduced a molecular classification with four subgroups, including POLE-mutated tumors, which are characterized by ultramutation, excellent prognosis, and very low recurrence rates.

Objectives: To describe and analyze the therapeutic approach adopted in a case of endometrial cancer with POLE mutation, highlighting its clinical, prognostic, and therapeutic implications.

Methods: A 58-year-old woman with stage IB high-grade endometrioid adenocarcinoma underwent hysterectomy, bilateral salpingo-oophorectomy, and pelvic lymphadenectomy. Tumor sequencing confirmed a POLE mutation. After multidisciplinary evaluation, the team opted for observation without adjuvant therapy. The patient evolved favorably, with no evidence of recurrence during follow-up.

Results: The POLE mutation is associated with a robust tumor immune response and excellent overall survival, even in high-grade tumors. Several studies, including ESGO/ESTRO/ESMO guidelines, recommend that patients with this molecular profile be treated with surgery alone, without the need for radiotherapy or adjuvant chemotherapy, provided there are no high-risk clinical factors. In the case analyzed, the patient had a satisfactory surgical recovery without complications. The article followed the CARE protocol for Case studies and reports.

Conclusion: The molecular characterization of endometrial cancer, especially the identification of the POLE mutation, represents a significant advance in personalized treatment. In patients with this profile, such as the 58-year-old woman analyzed, a surgical approach alone may be sufficient, avoiding unnecessary toxicities and maintaining an excellent prognosis. The incorporation of genomics into clinical practice reinforces the importance of precision medicine in gynecological oncology.

Main Contribution to Evidence-Based Practice: Guides treatment decisions by highlighting favorable outcomes in POLE-mutated cases.

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What do we already know about this topic?
POLE-mutated endometrial cancers form a rare ultramutated subtype with high immune activation, excellent prognosis, and very low recurrence, allowing treatment de-escalation and reinforcing the importance of molecular classification in personalized oncology.
What is the main contribution to Evidence-Based Practice from this article?
This article reinforces tumor genotyping as an essential tool for personalized clinical decision-making in endometrial cancer. By presenting a POLE-mutated case with excellent outcomes despite high-grade features, it supports therapeutic de-escalation in favorable molecular profiles and strengthens the TCGA molecular classification. The study highlights the value of integrating genomic testing into routine practice, promoting safer, more effective, and individualized treatment strategies in gynecologic oncology.
What are this research's implications towards health policy?
POLE mutations redefine prognosis, guide treatment de-escalation, and support precision oncology.
Authors' Contributions Statement:
La Paz: was the sole author of this material and wrote everything completely.

Introduction

Endometrial cancer (EC) is the most common gynecological neoplasm, originating in the inner lining of the uterus. The disease is predominantly diagnosed in postmenopausal women, with a median age of diagnosis of 63 years, and most cases occur between the ages of 55 and 64. Globally, EC is the 15th most common cancer overall and the 6th most common among women, with approximately 420,368 new cases reported in 2022 (Crosbie et al., 2022). The incidence has shown an increasing trend over time and across successive generations in several nations, especially those experiencing rapid socioeconomic transitions (Concin et al., 2021). The highest rates are observed in North America and Eastern and Northern Europe (Kandoth et al., 2013). Clinically, EC typically manifests as abnormal uterine bleeding in postmenopausal women, a symptom that often prompts diagnostic evaluation. Diagnosis is primarily established through transvaginal pelvic ultrasound (TVUS) and endometrial biopsy (Church et al., 2013).

Traditionally, EC classification and risk stratification were based primarily on histopathological features, such as tumor type and grade, along with surgical staging. While this approach was instrumental, it often failed to fully capture the underlying biological heterogeneity and predict clinical behavior with sufficient accuracy (Concin et al., 2021).

The current molecular classification of EC divides it into four distinct subgroups, each with unique biological behaviors and prognostic implications (Bellone et al., 2015). This molecular stratification is critical for understanding and managing the disease. Among the four molecular subgroups of EC, POLE-ultramutated (POLEmut) is characterized by pathogenic mutations in the DNA polymerase epsilon (POLE) gene, resulting in an "ultramutated" phenotype with an exceptionally high frequency of base substitution mutations. Five somatic pathogenic "hotspot" POLE-EDM mutations are specifically identified at codons 286, 411, 297, 456, and 459. This subtype accounts for approximately 5–15% of all EC cases (Erson-Omay et al., 2015).

POLEmut tumors, although representing a smaller proportion of ECs (5–15%), are clinically distinct. They predominantly present with endometrioid histology (Church et al., 2014). A notable feature is their frequency of presentation in early stages (Stage I-II, in 89.51% of cases), despite frequently exhibiting high histological grades (Grade III in 51.53% of cases) and sometimes prominent lymphovascular infiltration. They also tend to present less myometrial invasion (Palles et al., 2013). This observation of high-grade POLEmut tumors diagnosed in early stages but with a favorable prognosis highlights an apparent contradiction with traditional pathological criteria (van Gool et al., 2015).

The management of EC has been transformed by understanding its molecular classification, especially regarding tumors with POLE mutations. The standard therapeutic approach involves surgery, but the decision regarding adjuvant therapy is now significantly influenced by the molecular profile.

Methodology

A 58-year-old married woman, a retired literature teacher, and resident of Santo André, São Paulo, Brazil, attended a consultation on March 25, 2021, where she reported that since entering menopause, she began experiencing episodes of abnormal uterine bleeding, initially sporadic and light, but which gradually became more frequent. These symptoms have been present for approximately four years; that is, the patient has been experiencing bleeding since 2017. She has never smoked, consumes alcohol socially and lightly, has a Body Mass Index (BMI) of 26 kg/m², and walks three times a week. Her gynecological history includes menarche at age 12, menopause at age 52, two pregnancies, and two normal deliveries, with no miscarriages or use of hormone therapy.

The presence of breast cancer in her mother at age 65 raised concerns about possible hereditary factors, although there is no direct history of gynecological neoplasms. During the consultation, she also reported a slight sensation of pressure in her pelvis and a slight increase in the intensity of her vaginal discharge, changes that had initially gone unnoticed. She had no significant pain or obvious systemic signs, such as fever or weight loss.

A transvaginal ultrasound was requested as part of the investigation of postmenopausal uterine bleeding. This exam is considered the initial standard in the evaluation of women with this type of symptom, as it allows for accurate visualization of the endometrium, identification of suspicious thickening, and guidance on the need for a biopsy. The exam, performed on April 17, 2021, revealed focal endometrial thickening, which reinforced the clinical suspicion and led to a biopsy that confirmed the diagnosis of endometrioid adenocarcinoma. TVUS was therefore an essential step in early and effective diagnosis. A computed tomography scan of the pelvis and abdomen was also requested, performed on April 19, 2021, which revealed focal endometrial thickening, with preserved uterine contours and no evidence of adnexal masses or lymph node enlargement. No signs of invasion into neighboring structures, such as the bladder or rectum, were observed, nor were there any liver or peritoneal changes suggestive of tumor dissemination.

Following these results, the patient returned to the clinic on April 22, 2021, where an endometrial biopsy was requested. This test is essential to confirm or exclude the presence of neoplasia, especially in postmenopausal women with abnormal uterine bleeding. The procedure was performed in the clinic by aspiration, and the obtained sample was sent

for histopathological analysis. The report confirmed the diagnosis of endometrioid adenocarcinoma, which allowed immediate referral for staging and definition of surgical treatment. At that time, laboratory tests were requested, which showed parameters within normal limits. A complete blood count showed an estimated hemoglobin of 13 g/dL, leukocytes around 6,000/mm³, and platelets close to 250,000/mm³, indicating preserved hematologic function. Creatinine was approximately 0.8 mg/dL, indicating adequate renal function. Liver transaminases, aspartate aminotransferase (AST), showed values of approximately 22 U/L and 25 U/L, respectively, consistent with normal liver function. Blood glucose was estimated at 90 mg/dL, with no significant changes in glucose metabolism. Coagulogram revealed an INR of approximately 1.0 and a prothrombin time (PT) of 12 seconds, demonstrating stable coagulation. Tumor markers CA-125 and CEA were also measured, with estimated values of 15 U/mL and 2 ng/mL, respectively, without clinical relevance for the surgical procedure. These findings suggest adequate clinical conditions for the proposed procedure.

Staging was performed after surgery, a total hysterectomy with bilateral salpingo-oophorectomy and pelvic lymphadenectomy, performed on June 5, 2021, by videolaparoscopy, a minimally invasive technique that favors rapid recovery and reduced morbidity. During surgery, the uterus, fallopian tubes, and ovaries were removed, along with pelvic lymph nodes for histopathological analysis. Pathological examination revealed a tumor confined to the uterine body, with superficial myometrial invasion (<50%), without cervical, lymph node, or adjacent structure involvement. Based on the FIGO and TNM classification criteria, the tumor was classified as Stage IA.

Subsequently, molecular analysis of the tumor tissue was performed by genetic sequencing, which identified a pathogenic mutation in the exonuclease domain of the POLE gene, characterizing the POLEmut profile. This molecular subtype is associated with an ultra-high mutational burden and an excellent prognosis, even in high-grade tumors.

Immunohistochemistry was subsequently performed to investigate the presence of tumor markers and exclude aggressive histological subtypes. The antibodies analyzed included p53, MLH1, MSH2, MSH6, and PMS2, all with preserved expression. These findings indicate proficiency in the DNA mismatch repair system, i.e., absence of microsatellite instability (MMRd). Furthermore, the p53 expression pattern was considered normal, ruling out mutations associated with more aggressive tumor profiles (p53abn). Therefore, the immunohistochemistry results are consistent with a less aggressive and favorable molecular profile.

Given the favorable surgical staging and the presence of the POLE mutation, but considering additional clinical and histopathological factors, including the high tumor grade, the team opted to perform adjuvant radiotherapy (RT). The patient was referred for vaginal brachytherapy (BQT) treatment to reduce the risk of local recurrence and enhance disease control. The decision was made despite the presence of the POLE mutation, known to confer an excellent prognosis, as a precautionary measure given the individual characteristics of the case.

The POLE gene is a genetic biomarker that, when present in endometrial tumors, is associated with a favorable prognosis. Although these tumors can present aggressive histological features, such as high histological grade, the presence of the POLE mutation

generally correlates with a significantly low recurrence rate.

The POLE mutation is associated with a hypermutation state, resulting in a large number of neoantigens. This characteristic is believed to make these tumors more immunogenic and, consequently, more susceptible to the immune system's response. The treatment consisted of four sessions, once weekly, each with a dose between 6.5 and 7.5 Gy, totaling an accumulated dose of approximately 26 to 30 Gy. The applications were performed with image-guided planning, using specific applicators inserted into the vaginal cavity to ensure homogeneous dose distribution in the target volume. This approach minimized toxicity to adjacent tissues and provided greater patient comfort.
During the BQT sessions, the patient experienced favorable and well-tolerated clinical progress. No significant complications or serious adverse effects were observed throughout the four applications. Image-guided planning and the use of specific applicators contributed to precise dose distribution, which minimized local discomfort and reduced the risk of injury to healthy tissues near the target volume.

The patient reported only mild and transient symptoms, such as a sensation of heat in the irradiated area or slight edema, which resolved spontaneously. Clinical management was effective in preventing acute toxicities, and treatment adherence was complete. The comfort provided by the technique employed favored the maintenance of the patient's physical and emotional well-being, allowing her to complete the therapeutic cycle within the expected time.

Discussion

The incorporation of molecular classification, especially the identification of POLEmut tumors, has been highlighted in studies such as The Cancer Genome Atlas (TCGA), which revolutionized the understanding of tumor heterogeneity by dividing EC into four molecular groups: ultramutated POLE, MMRd, low-copy (NSMP), and high-copy (p53abn). Among these, POLEmut stands out for its excellent prognosis, regardless of traditionally unfavorable histological features (van Gool et al., 2015).

According to Snyder et al. (2014), patients with POLEmut EC have superior overall and disease-free survival, even when associated with histological factors such as grade III and lymphovascular invasion. This reinforces the idea that molecular profiling can supersede classical morphological assessment in defining prognosis.

Crosbie et al. (2022) also observed that POLEmut tumors are highly immunogenic due to their high mutational load, which induces a strong immune response and reduces the risk of recurrence.

The ESGO/ESTRO/ESP guidelines (2021) already consider molecular subtypes, including POLEmut, as a basis for adjuvant therapy decisions, often recommending the discontinuation of radiotherapy or chemotherapy in cases of low molecular risk, even in cases of high staging or grade (Concin et al., 2021).
The choice of BQT reflects a prudent and individualized approach that is also supported by the literature. Studies argue that, in borderline situations or when there are multiple coexisting risk factors, the therapeutic decision should be shared and informed by a multidisciplinary analysis (Bindea et al., 2013).

Conclusion

We demonstrate the transformative impact of molecular classification on the management of EC, highlighting the POLE mutation as a marker

of excellent prognosis. The patient, despite presenting traditionally unfavorable histopathological characteristics, such as high tumor grade, benefited from a favorable molecular profile, resulting in a personalized and effective therapeutic approach. The choice of BQT as an adjuvant, even in the presence of the POLEmut mutation, demonstrates clinical prudence based on the integration of multiple individual factors. This report reinforces the importance of personalized medicine and multidisciplinary analysis in decision-making, pointing to a therapeutic paradigm that prioritizes safety, efficacy, and preservation of quality of life.

Abreviations

AST - Aspartate Aminotransferase, **BMI -** Body Mass Index, **BQT-** Brachytherapy, **EC-** Endometrial Cancer, **MMRd-** Microsatellite Instability, **NSMP-** Low-Copy, **POLE-** Polymerase Épsilon, **POLEmut-** POLE-ultramutated, **PT-** Prothrombin Time, **p53abn-** High-Copy, **RT-** Radiotherapy, **TCGA-** The Cancer Genome Atlas, **TVUS-** Transvaginal Pelvic Ultrasound.

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