Neuroendocrine Transformation in Gynecologic Malignancy

A Case report Highlighting the Role of Molecular Profiling

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Background

-Primary neuroendocrine tumors account for less than 2% of gynecologic malignancies.
-Neuroendocrine transformation has been well described in lung and prostate cancers, it is uncommon in gynecologic malignancies, with only limited numbers of case reports in literature.
-We present a case of integrating molecular profiling to assess for transformation to neuroendocrine carcinoma and guide treatment decision.

Methods

We present a 41-year-old woman with FIGO stage II endometrioid adenocarcinoma of the right ovary arising in a background of endometriosis.
Comprehensive genomic profiling of the primary tumor demonstrated KRAS, PTEN, and CTCF alterations, with low tumor mutational burden (TMB-low), microsatellite-stable (MSS) disease, negative folate receptor alpha (FOLR1) expression, and equivocal HER2 expression (2+).
She underwent primary treatment followed by six cycles of adjuvant carboplatin and paclitaxel.
Post-treatment surveillance imaging identified a new lytic lesion involving the left iliac bone with extension into the superior acetabulum. Biopsy of the lesion revealed metastatic poorly differentiated high-grade carcinoma with morphologic features distinct from those of the primary ovarian tumor.
Immunohistochemical evaluation demonstrated synaptophysin positivity, supporting neuroendocrine differentiation.
Comprehensive genomic profiling of the metastatic lesion revealed retention of the previously identified KRAS, PTEN, and CTCF alterations, but also demonstrated a strikingly different molecular profile, including high tumor mutational burden (TMB-high), microsatellite instability-high (MSI-high) status, and a TP53 alteration.
The marked morphologic and molecular discordance between the primary ovarian tumor and metastatic lesion raised two competing diagnostic considerations:
(1) an occult second primary high-grade neuroendocrine carcinoma, or
(2) histologic transformation of the original ovarian endometrioid carcinoma into a high-grade neuroendocrine carcinoma.
Given the aggressive clinical behavior and neuroendocrine features, the patient was treated with carboplatin, etoposide, and atezolizumab. Follow-up imaging has demonstrated a favorable radiographic response to therapy.

Case Presentation

Initial Diagnosis

41-year-old female diagnosed with FIGO stage II endometrioid adenocarcinoma of the right ovary in the setting of endometriosis.

Primary Tumor Genomic Profiling

- KRAS mutation
- Low tumor mutational burden (TMB)
- Microsatellite stable (MSS)
- FOLR1 negative
- HER2 equivocal (2+)

Treatment of Primary Tumor

Completed six cycles of adjuvant carboplatin and paclitaxel.

Post-Treatment Imaging

New lytic lesion in the left iliac bone extending into the superior acetabulum.

Biopsy of Metastatic Lesion

Poorly differentiated high-grade carcinoma with synaptophysin positivity, supporting neuroendocrine differentiation.

Genomic Profiling of Metastatic Lesion

High TMB, MSI-high status, and a genomic profile distinct from the primary tumor.

Diagnostic Considerations

1. Occult second primary high-grade neuroendocrine carcinoma.
2. Histologic transformation of the original ovarian endometrioid carcinoma into high-grade neuroendocrine carcinoma.

Treatment

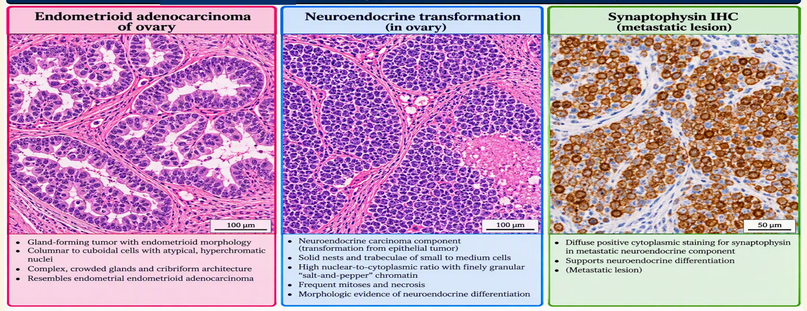
Initiated carboplatin, etoposide, and atezolizumab due to aggressive clinical behavior and neuroendocrine features.

Response

Follow-up imaging demonstrated a favorable response to therapy.

Results

Histology and immunochemistry

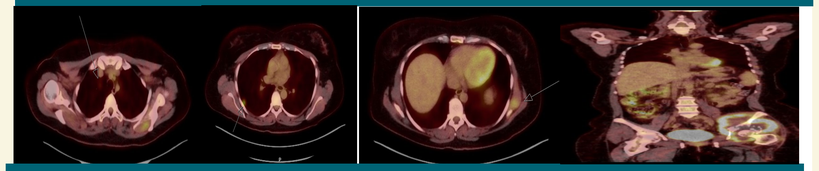


Comparison of Molecular Profiling (Tempus)

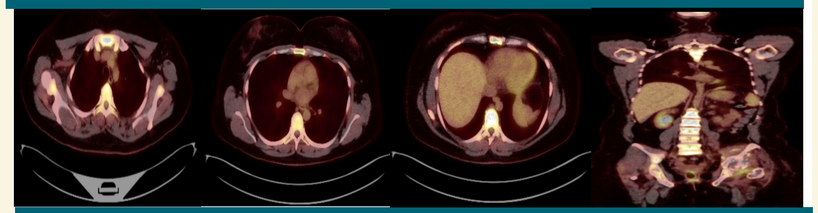
Genomic Alteration / Biomarker	Primary Ovarian Endometrioid Carcinoma	Metastatic High-Grade Carcinoma (Neuroendocrine Differentiation)
KRAS	p.G12D	p.G12D
PTEN	p.R130Qfs*4; p.R130G	p.R130Qfs*4; p.R130G
CTCF	p.H489Qfs*3	p.H489Qfs*3
TP53	p.Y163C	p.G244D
Tumor Mutational Burden (TMB)	Low	High
Microsatellite Instability (MSI)	Stable (MSS)	High (MSI-H)
Interpretation	• Shared KRAS, PTEN, and CTCF alterations support a common clonal origin of the primary and metastatic tumors. • The distinct TP53 alteration and differences in TMB/MSI status suggest molecular evolution during disease progression. • These findings support clonal evolution but do not independently establish the precise mechanism or timing of neuroendocrine transformation.	

MSS = microsatellite stable; MSI-H = microsatellite instability-high.
Values are transcribed from the provided Tempus reports.

PET scan before treatment



PET scan after treatment



Discussion

The molecular findings strongly favor neuroendocrine transformation through clonal evolution and lineage plasticity of the original endometrial carcinoma rather than a de novo neuroendocrine malignancy.

- **Shared PTEN alterations support a common clonal origin.**
  The primary endometrial carcinoma and neuroendocrine-transformed tumor harbored two identical PTEN mutations, making an independent de novo neuroendocrine neoplasm highly unlikely. While PTEN alterations are common in endometrial carcinoma, they are rarely reported in de novo neuroendocrine tumors, particularly as matching dual PTEN mutations.
- **Identical KRAS p.G12D mutation further supports clonal evolution.**
  Both tumors demonstrated the same KRAS p.G12D hotspot mutation. Although KRAS mutations may occur in de novo neuroendocrine neoplasms, the presence of an identical KRAS alteration in both specimens is unlikely to represent a coincidental independent event and instead supports derivation from the original endometrial carcinoma.
- **Emergence of new TP53 and CTCF alterations suggests treatment-driven clonal selection.**
  The neuroendocrine-transformed tumor acquired TP53 p.G244D and a distinct CTCF alteration, differing from the TP53 p.Y163C and CTCF mutations identified in the primary tumor. These findings are consistent with clonal selection and genomic evolution under chemotherapy pressure, leading to the emergence of a treatment-resistant neuroendocrine phenotype