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Case study

Corded and hyalinized mesonephric-like adenocarcinoma of the uterine corpus: report of a case mimicking endometrioid carcinoma☆

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Summary Mesonephric-like adenocarcinoma is a recently described adenocarcinoma of the uterine body and ovary with overlapping features of mesonephric adenocarcinoma and endometrioid carcinoma. It is thought to be a mullerian adenocarcinoma that has differentiated along mesonephric lines. A 71-year-old woman had a 3-cm endometrial mass that invaded the myometrium without gross or microscopic evidence of cervical involvement. The tumor had a variety of architectural patterns and produced prominent stromal hyalinization containing embedded cords and trabeculae of tumor cells. No squamous or mucinous differentiation or associated mesonephric remnants or hyperplasia was identified. The tumor was positive for TTF1 and GATA3, very focally and weakly positive for estrogen receptor and negative for progesterone receptor and nuclear expression of β-catenin. An unusual inverse pattern of TTF1 and GATA3 immunoreactivity was observed. DNA analysis by digital droplet polymerase chain reaction and quantitative polymerase chain reaction identified an activating *KRAS* (G12A) mutation. The tumor was interpreted as corded and hyalinized mesonephric-like adenocarcinoma that mimicked corded and hyalinized endometrioid carcinoma.

1. Introduction

Corded and hyalinized endometrioid carcinoma (CHEC) is the descriptive name proposed by Murray et al [1] in 2005 for a spectrum of endometrioid carcinomas of the uterine corpus that have cords of epithelioid cells, spindled cells, and/or fusiform cells with or without coinciding production of a dense hyaline matrix. These corded and hyalinized components intermix or blend with conventional endometrioid carcinoma and give the appearance of a biphasic carcinoma that may be confused with malignant mixed mullerian tumor (MMMT). However, in contrast to MMMT, which is high grade and clinically aggressive, most endometrioid carcinomas with corded and hyalinized elements are International Federation of Gynecology and Obstetrics (FIGO) grade 1 or 2 and early stage, and patients have a generally favorable prognosis [1,2]. Because of increased awareness of their clinical significance, corded and hyalinized elements in an otherwise low-grade carcinoma of the uterine body tend to be considered essentially diagnostic of CHEC.

Mesonephric-like adenocarcinoma (MLA) is a recently recognized adenocarcinoma of the uterine corpus and ovary characterized in 2016 by McFarland et al [3] in a series of 12 cases. MLA of the uterine corpus has considerable morphologic and

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immunohistochemical overlap with conventional mesonephric adenocarcinoma, but is differentiated from conventional mesonephric adenocarcinoma, a tumor of wolffian origin, by consistently originating/involving the endometrium, lacking associated mesonephric remnants or hyperplasia, and infrequently involving the uterine cervix.

A follow-up study by Mirkovic and investigators [4] profiled 7 of these reported cases by targeted hybridization capture next-generation sequencing and compared data with an earlier targeted genomic profiling study of mesonephric adenocarcinomas of the female genital tract published by the same group [5]. Although MLA had recurrent *KRAS* mutations and copy number signatures similar to mesonephric adenocarcinoma, MLA carried *PIK3CA* mutations in nearly half of the cases, a mutation not found to date in mesonephric adenocarcinoma. Furthermore, *PIK3CA* aberrations are among the most frequent genetic alterations in endometrioid carcinoma [6,7]. From accrued data, the authors suggested that MLA is a mullerian adenocarcinoma that has differentiated along mesonephric lines.

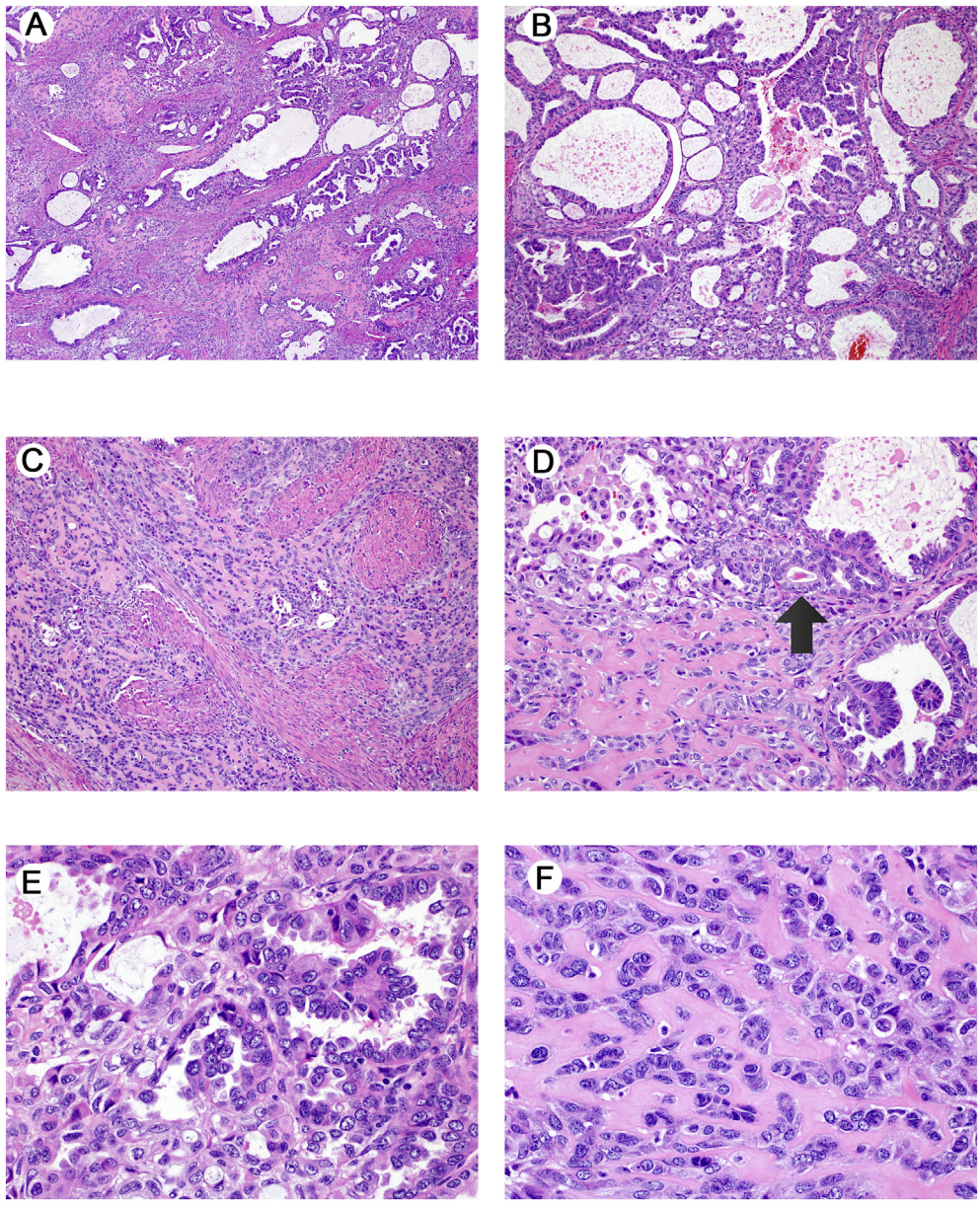

Fig. 1 The tumor involved endometrium and infiltrated the myometrium (A); manifested an array of growth patterns including ductal, papillary, and tubular structures (B); and produced zones of stromal hyalinization embedded by tumor cells arranged in cords and trabeculae (C). D, Occasional neoplastic ductal elements contained intraluminal eosinophilic material. E and F, Cytologic atypia was uniformly low grade, and the cells were generally cuboidal to columnar with moderate to scant eosinophilic cytoplasm and ovoid nuclei containing clear to fine, vesicular chromatin. E and F, Nuclear overlap was common and nuclear grooves were present.

Table Antibody panel

Antigen	Clone	Dilution	Manufacturer
TTF1	SPT24	1:200	Leica (Buffalo Grove, IL)
TTF1	8G7G3/1	1:50	Dako (Santa Clara, CA)
GATA3	L50-823	1:200	Biocare (Rocklin, CA)
ER	SP1	Prediluted	Ventana (Tucson, AZ)
PR	1E2	Prediluted	Ventana
β-Catenin	14	Prediluted	Cell Marque (Rocklin, CA)
PAX8	SP348	1:100	Abcam (Cambridge, MA)
p53	DO-7	Prediluted	Ventana
MLH1	ES05	1:25	Dako
PMS2	EPR3947	1:100	Biocare
MSH2	FE11	1:100	Biocare
MSH6	BC/44	1:50	Biocare

The Bond-III (Leica) platform was used for MSH2; the BenchMark XT (Ventana) platform was used for all other antibodies.

We present the morphologic, immunohistochemical, and molecular genetic findings of an adenocarcinoma of the uterine body that mimicked CHEC and we believe is the first description of corded and hyalinized MLA.

2. Case report

A 71-year-old woman presented to an outside facility for surgical management of endometrial cancer. She underwent total hysterectomy and bilateral salpingo-oophorectomy. Gross findings in the hysterectomy specimen revealed a 3 × 2 × 2-cm light tan to focally maroon mass in the endometrium that appeared to invade into the outer half of the myometrium. No gross evidence of cervical involvement was present. The case was sent for consultation with a working diagnosis of FIGO grade 2 endometrioid carcinoma with unusual features.

Sections of the tumor showed an endometrial adenocarcinoma that infiltrated the myometrium in an array of architectural patterns and produced prominent stromal hyalinization (Fig. 1A). The tumor formed a variety of ductal, papillary, and tubular elements that often merged into densely and morphologically heterogeneous epithelial structures (Fig. 1B). Numerous segments of epithelium were attenuated (Fig. 1B). Stromal hyalinization containing cords and trabeculae of embedded tumor cells was identified throughout all regions of the tumor and comprised approximately 30% of the overall mass (Fig. 1C). A few ducts contained intraluminal eosinophilic material (Fig. 1D), and all of these exhibited the same degree of cytologic atypia as the other neoplastic components. Cytologic atypia was uniformly low grade. The cells were generally cuboidal to columnar and had moderate to scant eosinophilic cytoplasm and ovoid nuclei containing clear to fine, vesicular chromatin (Fig. 1E and F). Nuclear overlap was common and nuclear grooves were present (Fig. 1E and F). Mitotic activity was relatively low level without atypical mitotic figures. Adenocarcinoma invaded into the outer half of the myometrium. Lymphovascular invasion was not identified. The cervix and right and left ovaries and fallopian tubes were negative for tumor. No squamous or mucinous differentiation, heterologous elements, necrosis, associated mesonephric remnants, or hyperplasia or associated endometrial hyperplasia was seen.

A panel of immunohistochemical stains was performed (Table). The tumor was positive for both clones of PAX8, TTF1 (SPT24 and 8G7G3/1), and GATA3; very focally and weakly positive for estrogen receptor (ER; <5% of cells); and negative for progesterone receptor (PR) and nuclear expression of β-catenin. p53 had a heterogeneous expression pattern throughout the tumor. Mismatch repair proteins were retained. Although portions of the tumor were equally positive for TTF1 and GATA3 in regard to intensity and distribution (Fig. 2A-C), there were differences in expression patterns of the corded and hyalinized component, as well as areas of the noncorded and hyalinized component. TTF1 (SPT24) was expressed by about 50% of the noncorded and hyalinized tumor cells in a patchy, strong intensity pattern and was entirely negative in the corded and hyalinized component. Similarly, TTF1 (8G7G3/1) was expressed by approximately 20% of the noncorded and hyalinized tumor cells in a patchy, weak-to-moderate intensity pattern and was totally negative in the corded and hyalinized component. GATA3 was positive in an estimated 60% of the tumor; expressed in a patchy, strong intensity pattern; and, in contrast to both clones of TTF1, was the only marker that was positive in the corded and hyalinized component (Fig. 2D-F).

Another unusual finding in several regions of the tumor was an inverse pattern of expression of TTF1 and GATA3: some typical epithelial elements were either entirely positive or negative for TTF1 (Fig. 2E), whereas these same elements were conversely negative or positive for GATA3 (Fig. 2F). The reason for this inverse pattern is not clear because there were no morphologic characteristics to associate with these different patterns. Furthermore, this observation has not been documented in previous examples of MLA.

DNA was extracted from paraffin-embedded sections of tumor and analyzed by digital droplet polymerase chain reaction

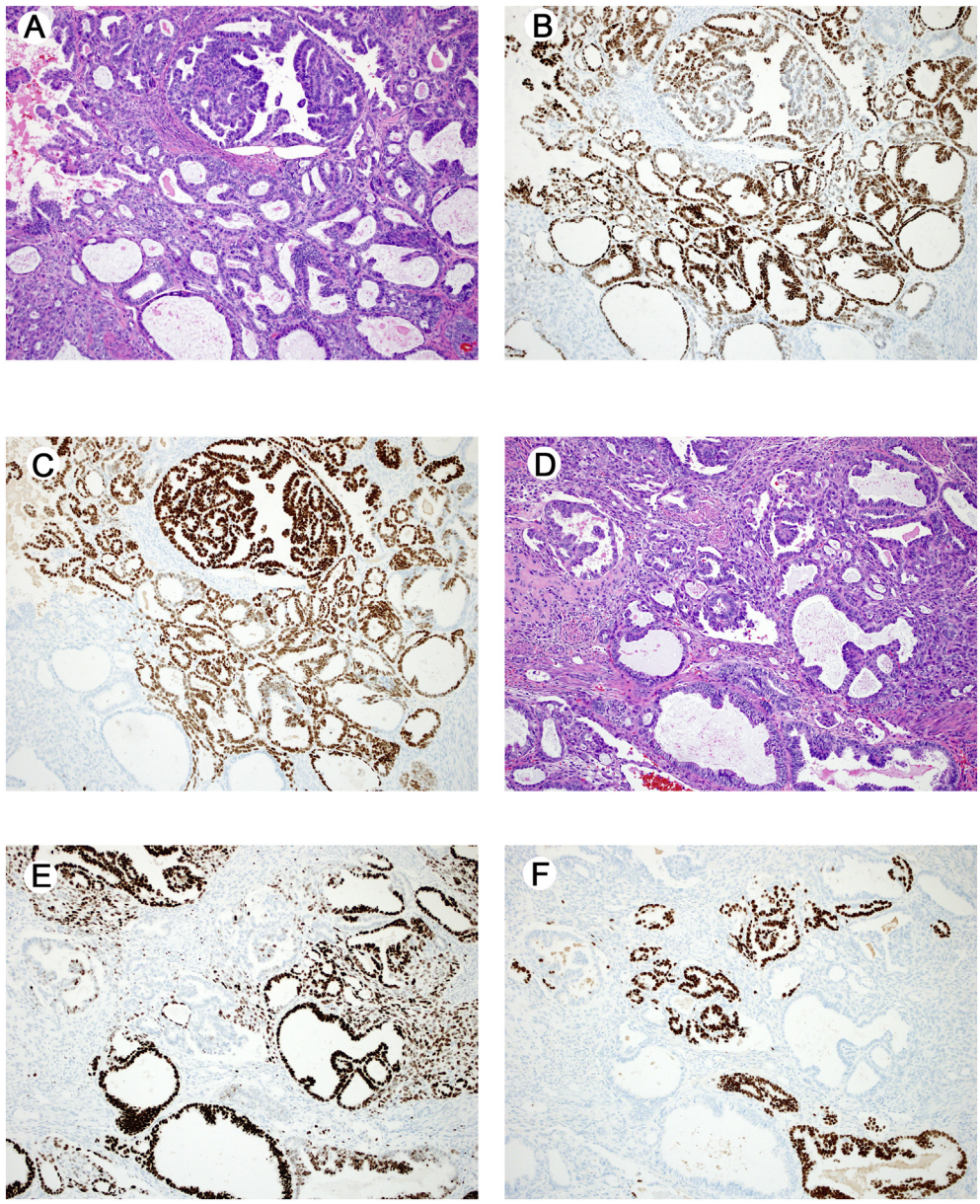

Fig. 2 A-C, Portions of the tumor exhibited equivalent and parallel expression of TTF1 and GATA3. However, there were differences in expression patterns in the corded and hyalinized component as well as the noncorded and hyalinized component. D-F, TTF1 (SPT24) and GATA3 showed an inverse pattern in parts of the tumor where one portion of epithelium was positive and the other was negative: TTF1 (SPT24) was conversely negative in GATA3-positive epithelium and positive in GATA3-negative epithelium (compare E [GATA3] and F [TTF1]). D-F, Furthermore, GATA3 was strongly positive in the corded and hyalinized component, but both clones of TTF1 were consistently negative in the corded and hyalinized component (compare E [GATA3] and F [TTF1]).

(PCR) and quantitative PCR for the presence of an activating *KRAS* mutation. A total of 4006 *KRAS* G12/13 mutant copies and 1695 *KRAS* G12/13 wild-type copies were identified by digital droplet PCR, yielding a fractional abundance of 70.3. The c.35G > C, p.Gly12Ala mutation was confirmed by quantitative PCR.

The tumor was classified as corded and hyalinized MLA. The case was a recent consult, and no additional follow-up is available.

3. Discussion

CHEC emerged as a variant of endometrioid carcinoma from a study of 31 cases of phenotypically heterogeneous tumors of the uterine corpus with unusual growth patterns including corded and trabecular arrangements of epithelioid and/or spindled cells often associated with a richly hyalinized matrix [1]. Although CHEC and MMMT are similar in their capacity to exhibit a spectrum of morphologic heterogeneity,

they diverge by the former's consistently low-grade carcinomatous elements, low-stage clinical presentation, and favorable patient outcomes in contrast to the latter's high-grade carcinomatous and sarcomatous components and frequently aggressive clinical behavior. Given the potentially significant therapeutic and prognostic implications of misclassifying CHEC as MMMT, awareness of corded and hyalinized elements in a low-grade carcinoma has led to these findings being strongly tied to CHEC.

MLA is a newly described adenocarcinoma of the uterine body and ovary. Reports of MLA are limited, with only 12 cases currently published, but data from 2 collaborative studies have established the foundational clinical, morphologic, immunophenotypic, and molecular genetic characteristics of these tumors [3,4]. From these studies, patient age ranged from 42 to 70 years, with a mean of 60 years. Gross features of MLA of the uterine corpus are incomplete, but all cases have demonstrated at least microscopic evidence of endometrial involvement with some examples described as grossly polypoid. Microscopically, MLA is consistently heterogeneous in its architecture (tubular, papillary, sieve-like, ductal, solid) with cuboidal to columnar epithelium and attenuated segments. Occasional small ducts or tubules can contain intraluminal eosinophilic sections. The cells tend to have frequently scant eosinophilic cytoplasm and ovoid to angulated nuclei that sometimes overlap and have longitudinal grooves. Nuclear features are low grade, with no greater than moderate cytologic atypia. No squamous or mucinous differentiation or mesonephric remnants or hyperplasia is present. Likewise, the immunophenotype of MLA is mostly consistent: all tumors are positive for CK7 (8 tested cases) and PAX8 (12 tested cases), all are negative for hormone receptors (ER, 12 tested cases; PR, 11 tested cases), and most (11/12) are positive for TTF1, usually diffusely. Less consistent is expression of CD10, GATA3, and calretinin: CD10 had varying luminal positivity in 7 (78%) of 9 tumors, GATA3 had variable positivity in 3 (27%) of 11, and differing quantities of calretinin positivity were found in 3 (50%) of 6. Of the 7 uterine primaries, 2 patients were staged as FIGO IA, 1 as IB, 1 as IIIC, and 1 as IV. The 2 IA tumors were both myoinvasive. The initial study of the clinical, morphologic, and immunohistochemical characteristics by McFarland and colleagues [3] concluded that these tumors were unique adenocarcinomas with overlapping morphologic and immunohistochemical qualities of mesonephric adenocarcinoma, demonstrated potential for advanced-stage presentation and recommended reporting such tumors as MLA.

Seven of these previously reported cases (4 ovarian, 3 uterine corpus) were subsequently investigated by targeted hybridization capture next-generation sequencing 2 years later by Mirkovic et al [4]. Activating *KRAS* mutations were identified in codon 12 of all 7 cases, *PIK3CA* mutations in 3 cases and no alterations of *PTEN*, *ARID1A*, or *TP53*. Furthermore, copy number analysis showed 1q gain in 3 cases, chromosome 10 gain in 4 cases, and chromosome 12 gain in 3 cases. A similar investigation of mesonephric adenocarcinomas of the female genital tract was published in 2015 by the same group [5]. Although MLA and mesonephric adenocarcinoma genetically share frequent mutation of *KRAS* (100% versus 75%, respectively), 1q gain (71% versus 75%), chromosome 10 gain (57% versus 31%), chromosome 12 gain (43% versus 31%), and lack mutation of *PTEN*, nearly half of the analyzed cases of MLA had a mutation in *PIK3CA*, an alteration that was not present in any mesonephric adenocarcinomas. In contrast to mesonephric adenocarcinomas, *PIK3CA* aberrations are among the most frequent genetic alteration in endometrioid carcinoma [6,7]. From morphologic, immunohistochemical, and molecular genetic data, the recent profiling study ultimately proposed MLA as a mullerian adenocarcinoma with mesonephric differentiation [4].

We interpreted the findings in our case to be those of corded and hyalinized MLA. Differentiating the tumor from CHEC is its heterogeneous architecture resembling mesonephric growth patterns, segments of attenuated epithelium, lack of squamous or mucinous differentiation, essentially negative hormone receptor expression, considerable positivity for TTF1 and GATA3, negative nuclear β-catenin expression (nuclear positivity in corded and hyalinized elements of CHEC was reported in 6/6 tested tumors with an underlying gene mutation in 4/4 tested tumors [8]), and retained mismatch repair protein expression. Although stromal hyalinization can focally occur in conventional mesonephric adenocarcinomas, other features of this tumor are inconsistent with most mesonephric adenocarcinomas by its mass-forming endometrial lesion, no involvement of the cervix, no evidence of associated mesonephric remnants or hyperplasia, and fairly extensive stromal hyalinization that contained cords and trabeculae of tumor cells. Lastly, despite the somewhat biphasic appearance of the tumor, neither high-grade carcinomatous nor sarcomatous components were present to justify classification as MMMT.

We believe that the clinicopathological findings in this case support current thinking that MLA is a mullerian adenocarcinoma exhibiting mesonephric differentiation given the tumor's overlapping features with endometrioid carcinoma and mesonephric adenocarcinoma. The frequency in which corded and hyalinized elements occur in MLA is unclear. Also unclear is the significance of inverse expression of TTF1 and GATA3. Further studies are necessary to establish the rate at which corded and hyalinized elements are found in MLA as well as the meaning, if any, the unique pattern of TTF1 and GATA3 immunoreactivity has in this tumor.

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