

Case Report

Metastatic Versus Primary Oncocytic Papillary Adenocarcinoma of the Endometrium: A Report of a Case and Review of the Literature

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Summary: We report a case of an oncocytic papillary adenocarcinoma of the endometrium in an 89-year-old female with vaginal bleeding. Imaging studies revealed lesions in the uterus, kidneys, pancreas, gluteus, and an enlarged portacaval lymph node. Diagnostic workup included an endometrial biopsy which showed malignant, oncocytic cells in a predominantly papillary pattern. These cells stained positive for epithelial markers (pan-cytokeratin, CK7, epithelial membrane antigen) and weakly for estrogen receptor. The cells were negative for cytokeratin 903, CAM 5.2, progesterone receptor, CD10, RCC Marker, CA-125, c-kit, and vimentin. Consultation with experts in Gynecologic and Genitourinary pathology returned a diagnosis of “adenocarcinoma compatible with metastatic renal cell carcinoma”—an intriguing possibility worthy of further exploration. To our knowledge, there are no reports in the literature of metastatic oncocytic papillary renal cell carcinoma to the endometrium. The clinical and pathologic features of oncocytic papillary endometrial lesions, including primary and metastatic processes, are reviewed. **Key Words:** Endometrium—Endometrium biopsy—Adenocarcinoma—Endometrioid carcinoma—Papillary adenocarcinoma—Oncocytic—Oxyphilic—Metastasis—Metastatic carcinoma—Papillary oncocytic metaplasia—Papillary oncocytic carcinoma—Renal cell carcinoma—Papillary renal cell carcinoma—Endometrioid adenocarcinoma with oncocytic metaplasia—Endometrioid carcinoma oxyphilic type—Endometrioid carcinoma with oncocytic change—Oncocytic endometrial carcinomas.

Primary endometrial carcinomas will often have a papillary architectural pattern and include serous adenocarcinoma, the villoglandular (papillary) variant of endometrioid adenocarcinoma and clear cell carcinoma. Oncocytic or oxyphilic change in the

endometrium has been described and when benign is often classified as a type of eosinophilic metaplasia (1). However, malignant papillary neoplasms of the endometrium with oncocytic or oxyphilic change are distinctly rare, with few reported cases in the literature (2–5).

In most patients with disease that is clinically and radiographically limited to the endometrium, pathologic interpretation of biopsied tissue is straightforward. However, in exceptional cases, during the workup for an endometrial malignancy, a metastatic neoplasm must be considered. In this report, we present a case of an 89-year-old woman with multiple mass lesions in her kidneys, pancreas, uterus and left gluteus, an enlarged portacaval lymph node, and

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a malignant oncocytic papillary adenocarcinoma identified on endometrial biopsy. Although expert consultation returned a diagnosis of "adenocarcinoma compatible with metastatic renal cell carcinoma," there was no tissue confirmation of a renal primary as the patient refused additional diagnostic studies. The clinical and pathologic features of oncocytic papillary endometrial lesions, including primary and metastatic processes, are reviewed.

REPORT OF A CASE

An 89-year-old woman who complained of a 1-day history of postmenopausal bleeding was evaluated after she was brought to the emergency department with hip pain. Her past medical history included multi-infarct dementia, diet controlled type II diabetes mellitus, atrial fibrillation, hypertension, depression, hypercholesterolemia, and idiopathic thrombocytopenic purpura. There was no history of renal or other genitourinary problems. Prior surgical procedures included a splenectomy in her 30s, parathyroidectomy for a benign adenoma, cholecystectomy, and a right oophorectomy at age 35 secondary to a "tumor." Previous pathology slides and/or reports were not available for review.

Physical examination revealed an obese hirsute elderly female. Speculum examination showed a polyp protruding from the cervical os and a portion was biopsied. Bimanual examination showed no masses or tenderness. Gross hematuria was identified and urine was sent for cytology.

Imaging Studies

Radiologic studies were performed and significant lesions were identified in the pelvis, right and left

kidneys, pancreas, a portocaval lymph node, and the gluteal region. Some studies were compared with studies 4 months prior.

Pelvic ultrasound (Fig. 1A) and computerized tomography (CT) scan with contrast showed an anteverted uterus with a markedly thickened heterogeneous endometrial cavity, a 4.2×2.4 cm lesion thought to represent either uterine or right adnexal pathology, and multiple leiomyomas. Adnexa were not visualized.

CT scan of the kidneys showed several lesions. On the right in the lower pole a 1.5 cm calcified lesion was identified, unchanged from the prior study. Ultrasound (Fig. 1B) showed the lesion to be complex with peripheral hypoechogenicity and an area of central high density, conforming to the CT criteria for renal cell carcinoma. On the left, CT scan showed multiple low attenuation lesions. The largest was 2.0×1.5 cm and had enlarged from 1.1×1.0 cm when compared with the prior study.

Also identified on CT scan were a 1.9 cm low attenuation cystic lesion in the body and a 1.4 cm lesion in the head of the pancreas, a 3.2×1.5 cm enlarged portocaval lymph node, and an incidental left gluteal lipoma, unchanged from the prior study.

Clinical Examination

Owing to concern for a gynecologic malignancy accompanied by gross hematuria, the patient was taken to the operating room for a gynecologic examination under anesthesia and cystoscopy. At that time, a Papanicolaou (PAP) smear of the cervix was obtained and biopsies of the endometrium and a 2×2 cm raised erythematous area in the bladder were performed.

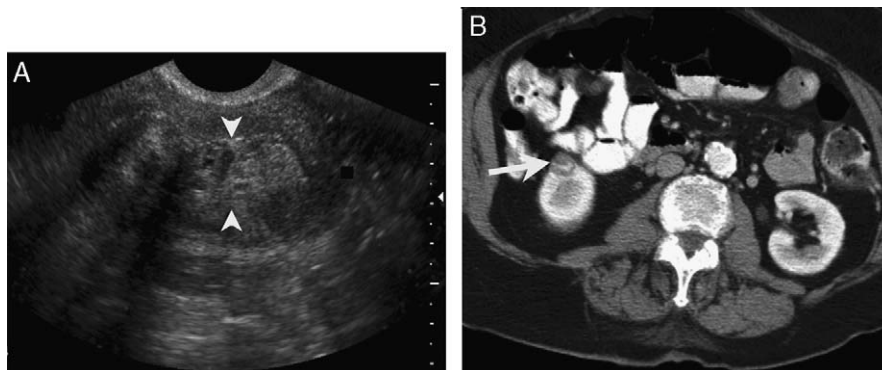


FIG. 1. A, Gray scale endovaginal sonogram in transverse view demonstrates a heterogeneous appearance of the endometrium with cystic change (arrowheads). Endometrium is markedly thickened and measures 2.38 cm. B, Contrast-enhanced computerized tomography (CT) in axial plane demonstrates an enhancing mass lesion in the lower pole of the right kidney (arrow), conforming to the CT criteria of renal cell carcinoma.

Pathologic Examination

Pathologic examination of the endometrial biopsy (Fig. 2) revealed predominantly mucus and blood with scattered neoplastic cells. The neoplastic cells were predominantly arranged in predominantly papillary and rare complex glandular structures of variable size. Both large and small papillae were lined by one or a few layers of neoplastic epithelial cells containing predominantly round to oval nuclei, irregular nuclear contours, a single prominent or multiple conspicuous nucleoli, distinct cell borders, and abundant, granular oncocyctic cytoplasm. Occasional cells contained greatly enlarged or hyperchromatic nuclei with clumped chromatin. Some cells appeared hobnailed and others contained a single intracytoplasmic oval, eosinophilic inclusion occasionally indenting the adjacent nucleus. A few

mitoses, rare lamellated psammoma bodies, scattered binucleated cells, and multiple apoptotic cells were also identified. Glandular areas contained similar neoplastic cells arranged back-to-back with little intervening stroma. No confluent necrosis was identified. The neoplastic cells stained strongly for pan-cytokeratin (AE1/AE3 and CAM5.2 cocktail), epithelial membrane antigen (EMA), cytokeratin 7 (CK7), weakly for estrogen receptor, and they were negative for cytokeratin CK903, cytokeratin CAM5.2, progesterone receptor, CD10, RCC marker, CA125, c-kit, and vimentin. This immunohistochemical profile would support a diagnosis of metastasis from a renal primary (6) and consultation with internationally known experts in Gynecologic and Genitourinary pathology returned a diagnosis of "adenocarcinoma compatible with metastatic renal cell carcinoma."

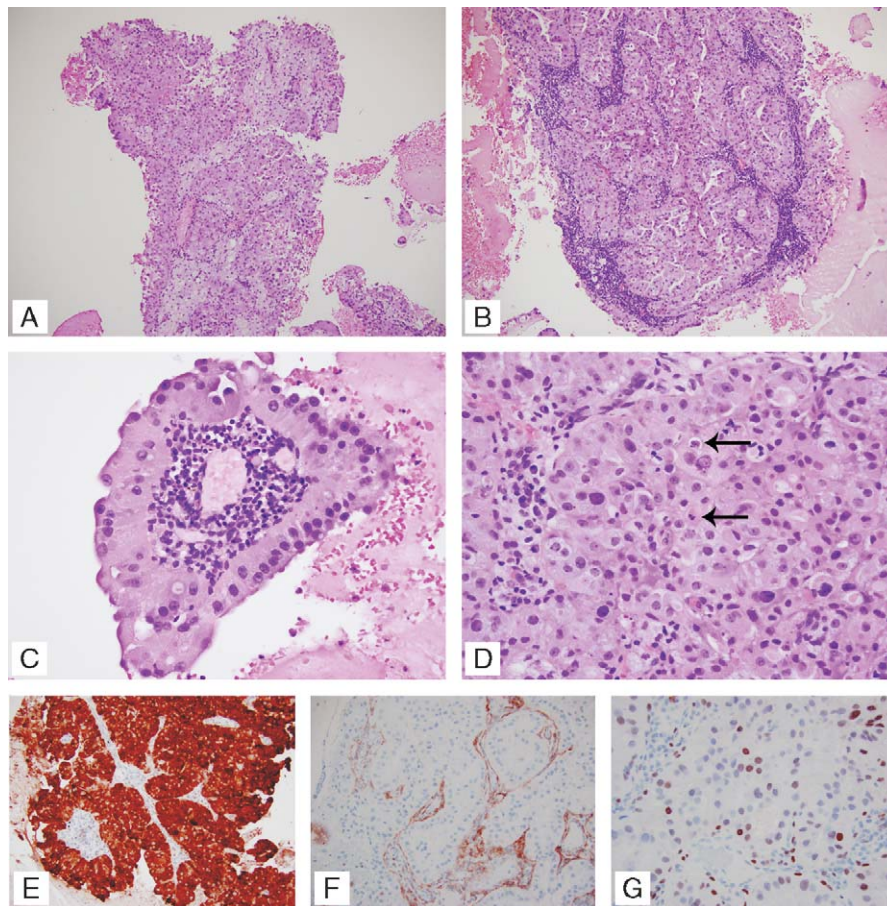


FIG. 2. Endometrium with oncocyctic papillary adenocarcinoma: tumor cells are arranged in (A) papillary and (B) complex glandular structures (original magnification: 100 ×). C, One or a few layers of oncocyctic epithelial cells contain predominantly round to oval nuclei with conspicuous nucleoli (original magnification: 400 ×). D, Apoptotic cells are present (arrows) and some cells have enlarged hyperchromatic nuclei (original magnification: 400 ×). Immunohistochemical stain for (E) epithelial membrane antigen is strongly positive (original magnification: 200 ×), (F) CD10 is negative (original magnification: 200 ×), and (G) estrogen receptor is positive (original magnification: 400 ×).

Microscopic examination of the cervical tissue revealed a benign endocervical polyp with microglandular hyperplasia. The PAP smear, bladder cytology, and bladder biopsy were all negative for dysplasia or malignancy.

Clinical Course

After the diagnosis of carcinoma was made, the patient chose to have no further treatment. Biopsies of the lesions in the pancreas, kidneys, and paracaval lymph node were not performed at the patients' request. She is alive after 3 years follow-up.

DISCUSSION

We report a rare oncocytic papillary adenocarcinoma diagnosed on endometrial biopsy in an 89-year-old woman who presented with multiple radiographic lesions in separate sites. Because of this clinical presentation, both primary and metastatic lesions were considered in the differential diagnosis.

Primary Endometrial Carcinomas With Papillary Features

Primary endometrial tumors that can present in a papillary pattern include serous adenocarcinoma, villoglandular carcinoma, and clear cell carcinoma (7). In comparison to the endometrial biopsy in our patient, the nuclei of papillary serous carcinoma are of much higher grade, mitoses are easily found, and individual detached cells may be found floating freely between papillae. Villoglandular endometrioid carcinoma has low-grade nuclei, similar to our case, arranged on long thin glandular stalks with scant fibrovascular stroma. However, oncocytic change in villoglandular carcinoma has not been reported. Clear cell carcinoma is similar to papillary serous carcinoma in that it usually has high-grade nuclei, and the cytoplasm contains characteristic clearing representing abundant glycogen. Focally, some cells can appear oxyphilic (5).

Primary Endometrial Carcinomas With Oncocytic Features

Although malignant carcinomas of the endometrium containing foci of papillary architecture are not uncommon, those with oncocytic features are distinctly rare. To our knowledge, only 9 primary endometrial oncocytic malignant neoplasms have

been reported in the literature: 1 endometrioid adenocarcinoma with oncocytic metaplasia (2), 3 endometrioid carcinomas—oxyphilic type (3), 1 "minimal deviation" endometrioid carcinoma with oncocytic change (4), and 4 oncocytic endometrial carcinomas (5) with areas of papillary architecture.

In a letter to the editor reporting a case of simple hyperplasia and a case of moderately differentiated adenocarcinoma with oncocytic change, Bergeron and Ferency (2) underlined the distinction between eosinophilic metaplasia and oncocytic (or "oxyphil") metaplasia. Eosinophilic metaplasia was thought to be due to increased number of ribosomes or intermediated filaments whereas oncocytic metaplasia was due to increased number of large mitochondria surrounded by ribosomes. The oncocytic nature of their cases was confirmed by electron microscopy (EM). Although EM was not performed in our case, the morphologic appearance of the tumor cells, showing cytomegaly with marked cytoplasmic granularity and eosinophilia, is characteristic of oncocytic change (Fig. 2C).

The 3 cases of endometrial endometrioid carcinomas, oxyphilic cell type, reported by Pitman et al. (3) are thought to be a distinct morphologic and clinical entity. The average patient age of Pitman's cases was 44.3 years. The lesional architecture was almost entirely glandular with no mention of papillary architecture. The cells lining each gland were large with abundant eosinophilic cytoplasm and low to intermediate grade nuclei focal areas of squamous differentiation. One of the 3 cases had marked mucin production and invaded the inner-third of the myometrium. The remaining 2 cases were low nuclear grade and had minimal to no invasion of the myometrium; however, 1 of these 2 was associated with bilateral ovarian endometrioid carcinomas. Although no immunohistochemical studies were performed in these cases some ovarian oxyphilic endometrioid carcinomas studied in the same report were positive for keratins and negative for carcinoembryonic antigen (CEA), EMA, S-100, desmin, HMB-45, and HCG. None of Pitman's cases contained abundant mitochondria when examined by EM. Follow-up was not entirely adequate, as 2 were recent cases, but 1 patient was alive with no evidence of disease at 6 years. In contrast to the endometrial biopsy in our patient, all of Pitman's cases had at least a focal tubular-glandular pattern consistent with endometrioid carcinoma.

The "minimal deviation" endometrioid carcinoma with oncocytic change reported by Mai et al. (4) was

identified in an 80-year-old woman who presented with postmenopausal spotting. The carcinoma was well differentiated with glands varying from simple and tubular to more complex and irregular, diffusely involving the entire thickness of the myometrium. Most glands were lined by epithelial cells with a bland cytologic appearance, containing abundant eosinophilic cytoplasm and secretory material. The appearance was similar to eosinophilic metaplasia; however, a small component of typical endometrioid carcinoma was identified. There was no lymphovascular invasion or desmoplasia, mitotic figures were not conspicuous, and cytologic atypia was mild. Mucin was identified, using periodic acid-Schiff and Alcian blue stains, along some luminal borders and within the cytoplasm of some tumor cells. An immunohistochemical stain for CEA was positive, flow cytometry showed a diploid population, and numerous mitochondria were identified by EM. In contrast to the endometrial biopsy from our patient, no papillary architecture was described in Mai's case.

The 4 oncocytic endometrial carcinomas published by Silver et al. (5) were also thought to be a distinct morphologic and clinical entity. They occurred in postmenopausal women, with a mean age of 64.5 years, and were not associated with recent exogenous hormone intake. All cases had areas with a papillary architecture and all were exclusively composed of neoplastic oncocytic cells. The neoplastic cells had eosinophilic, granular cytoplasm and formed a single layer lining each papillary core or gland lumen. Two of the cases contained tumor cells with intracytoplasmic mucin. In contrast to Pitman's cases, 3 of Silver's cases showed deep myometrial invasion and 2 demonstrated lymphovascular invasion. Conspicuous nucleoli, vesicular chromatin, and an average of 3 mitoses/10 high-power fields were thought to distinguish oncocytic carcinoma from oncocytic metaplasia. Oncocytic carcinoma was also favored over metaplasia when immunohistochemical stains showed strong p53 positivity, absence of staining for estrogen and progesterone receptors, and a Ki-67 labeling index of 14% to 33%. One carcinoma was estrogen receptor-positive, 1 was HER2-positive, and 1 was pCEA-positive. EM confirmed accumulation of mitochondria and free ribosomes in the cytoplasm. The endometrial biopsy in our patient was morphologically similar to Silver's endometrial oncocytic lesions. Our case, however, was predominantly papillary, contained only rare mitotic figures, the chromatin was not vesicular, and the estrogen receptor was positive by immunohistochemistry.

Although p53 and Ki-67 were not performed, the presence of atypia and single cell necrosis supported our diagnosis of carcinoma.

Although no standard exists for grading these oncocytic/oxyphilic tumors, most appear to be well-differentiated histologically and of low nuclear grade. Unfortunately, their rather bland histologic appearance does not always translate into their invasive potential. Three cases in the Silver et al. series were associated with deep myometrial invasion, 1 in the Pitman et al. series invaded into the inner one-third of the myometrium, and the case reported by Mai et al. extensively invaded the myometrium.

Metastatic Carcinomas to Endometrium

In contrast to primary malignant tumors of the endometrium, carcinoma metastatic to the endometrium is incredibly rare. In one study, only 325 metastatic tumors to the female genital tract were identified out of approximately 445,000 accessioned cases (8). Of these 325, only 15 were metastatic to the endometrium. Eight were from genital primaries (5 ovarian and 3 fallopian tube) and 7 from extragenital primaries (2 breast, 2 colon/rectum, 1 appendix, 1 stomach, and 1 uncertain). Four of the primaries that metastasized to the endometrium also involved a second genital site. It is not known how many of these endometrial metastases had papillary or oncocytic architecture.

In another study, Kumar and Hart (9) reviewed 63 surgical and autopsy cases of metastasis to the uterine corpus from extragenital cancers. Primary tumors metastatic to the uterus included breast (27 cases), colon (11 cases), stomach (7 cases), pancreas (7 cases), gallbladder (3 cases), lung (3 cases), melanoma (2 cases), bladder (2 cases), and thyroid (1 case). In 52 cases where the anatomic distribution of metastases within the uterine corpus could be evaluated, 32.7% (17/52) involved the endometrium and the myometrium, and only 2 involved the endometrium alone. When the metastases were located in the endometrium, they were mostly found in the stroma adjacent to normal endometrial glands. In 5 of the surgical cases (25% of total cases—4 curettage specimens and 1 hysterectomy), uterine metastases were the first indication of an extragenital primary tumor. However, in most cases the endometrium was not the only site of metastases, suggesting that when extragenital tumors do metastasize to the uterus it is usually a marker of widespread rather than focal disease (8–12). This is

supported by the fact that most patients with uterine metastases have a dismal prognosis, surviving only months to a few years (8–12).

Given the radiographic and clinical data on our patient, we felt that the lesion in the right lower pole of the kidney had the most potential to be malignant. Our search of the literature found only 3 reported cases of renal cell carcinoma metastatic to the endometrium (11,13). One was metastatic to both the endometrium and skin and was a conventional (clear cell) renal cell carcinoma (13). The others were included in a review from 1941 and the histologic subtype was not specified (11). Hence, no cases of metastatic papillary renal cell carcinoma to the endometrium have been described.

The possibility that our patient had a metastasis from an ovarian primary was also considered. As she had a prior oophorectomy for a “tumor” of unknown type and 1 of the current lesions identified by CT was situated near an ovary, this may represent an ovarian papillary carcinoma of either the oncocyctic or serous types. These tumors can look morphologically identical to their endometrial counterparts (5,7).

In summary, oncocyctic papillary carcinoma of the endometrium is a rare tumor. When reflecting on the site of origin in a patient who has multiple lesions in clinically separate sites, consideration should be given to the possibility of metastasis. In our case of an oncocyctic papillary adenocarcinoma in an endometrial biopsy of an 89-year-old female, the differential diagnosis includes primary endometrial carcinoma and metastasis from either a renal or adnexal primary. Our patients’ preference to forgo further diagnostic procedures prevented us from either confirming or eliminating the possibility of metastasis. However, despite her indolent clinical course and the lack of tissue

confirmation, metastatic carcinoma is a distinct possibility based on the radiographic, morphologic, and immunohistochemical findings and should be seriously entertained.

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