A rare case of invasive mucinous adenocarcinoma of fallopian tube fimbria with metastasis to ipsilateral ovary, uterine serosa, myometrium and pelvis: Case report and review of literature

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Abstract Mucinous adenocarcinoma of the fallopian tube is exceptionally rare and the detailed clinicopathologic features of these tumors have not yet been reported in English literature. Here we report a moderately differentiated mucinous adenocarcinoma arising in the tubal fimbria in a 70-year-old woman. Patient had a history of cholecystectomy for gallstones and gastric banding who presented with gastrointestinal discomfort and was found to have a large adnexal mass on imaging studies. Serum CA-125 was moderately elevated. Recent mammography, upper endoscopy and colonoscopy were completely normal. She underwent surgical staging for the adnexal mass. Frozen section and final pathology diagnosis revealed moderately differentiated adenocarcinoma arising in the left fimbria. Carcinoma had spread to the ipsilateral ovary and pelvic soft tissue at the time of her presentation. Tumor was strongly immunoreactive to CK7 and CEA, and was negative for CK20, CDX-2, PAX-8, WT-1, p16, ER, and vimentin. TP53 showed wild-type phenotype by immunohistochemistry. Molecular studies showed no mutation in codon 12 and 13 of the k-ras gene, and no mutation was detected in the BRAF and EGFR genes. In addition, the non-tumorous fimbria epithelium showed a spectrum of mucinous alterations with variable nuclear atypia: cytologically bland areas that were reminiscent of...
mucinous metaplasia were positive for p53 and showed minimal proliferation as assessed by Ki-67, and cytologically atypical stratified mucinous epithelium that was positive for p53 and Ki-67. The patient received 3 cycles of Folfox and was regularly followed at a 3–6 month interval. Her carcinoma recurred in abdomen at 32 months post surgery. After excluding the possibility of an extra-gynecologic tract primary through extensive clinical investigations and post-surgical follow-up, we concluded that this tumor most likely represented a mucinous adenocarcinoma of tubal origin.

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1. Introduction

Primary fallopian tube carcinomas have traditionally been considered rare tumors, with a reported average annual incidence in the United States of 3.6 per million women per year [1]. However, the incidence appears to be increasing, an expected consequence of the recent paradigm shift that ascribes a tubal origin to a significant proportion of ovarian and pelvic epithelial carcinomas [2,3]. Most fallopian tube carcinomas are of serous type, followed by the endometrioid type [4–13]. Mucinous adenocarcinomas are exceptionally rare in the fallopian tube, and we are aware of only 3 cases previously reported in the English literature [6,8]. We describe herein a case of an advanced-stage invasive mucinous adenocarcinoma arising in tubal fimbria and review the relevant literature.

2. Materials and methods

2.1. Case history

A 70-year-old female gravida 3, para 3 with last menstrual period at age 44 presented to her primary care physician with gastrointestinal discomfort. Her medical history was remarkable for hypertension, Type II diabetes, and lichen sclerosis. She was on Evista 60 mg daily. She had a history of cholecystectomy, appendectomy, coronary artery bypass graft, gastric banding, and bilateral tubal ligation at age 32. Recent mammogram, colonoscopy and papanicolaou tests were all within normal limits. At current presentation, her physical examination was unremarkable. A chest and abdominal computerized axial tomography (CT) with contrast showed dilated esophagus due to tight gastric banding and a lobulated fluid attenuation (12.3 × 9.9 cm) in the left pelvis, which was separated from the uterus. Lungs, liver, pancreas, kidneys, spleen and bowel were normal. A pelvic ultrasound confirmed a 13 × 9.2 × 9 cm multi-septated complex mass in the left adnexa. Pre-operative serum CA-125 was elevated to 213 (normal <34). Serum CEA was normal at 0.8 ng/ml (normal 0–3.8). The patient underwent an exploratory laparotomy and resection of the left adnexal mass.

Intraoperative frozen section of the mass was performed, and a diagnosis of mucinous adenocarcinoma was made. A complete surgical staging with hysterectomy, salpingo-oophorectomy, omentectomy, paraaortic and pelvic lymph node dissection was thus performed. She received 3 cycles of adjuvant chemotherapy with Folfox (folinic acid, 5-FU and Oxaliplatin). She was followed with serum CA-125 every 1–3 months during the first year post-surgery, which showed steady decline to the normal level. Other post-operative follow-up included chest and abdominal CT with contrast every 6 months, all of which were normal until the most recent study at 32 months which showed mesenteric nodularity in the anterior mid abdomen, involving the gastrocolic ligament, and in the right paracolic gutter, consistent with carcinomatosis, and an infiltrating soft tissue mass in the midline of the mid anterior abdominal wall, measuring 2 × 1.6 × 4.3 cm. The patient is currently alive with recurrent disease at 34 months post-surgery.

2.2. Histology and immunohistochemistry

Tissue sections were fixed in 10% neutral buffered formalin, embedded in paraffin, sectioned at 4-μm thickness, and stained with hematoxylin and eosin. Mucin stain and the immunohistochemistry were evaluated at the Histology and Immunopathology Laboratory of Long Island Jewish Medical Center (North Shore-LIJ Health System, New Hyde Park, NY), where the Ventana BenchMark Autostainer (Ventana Medical System, Tucson, Arizona) was used on 4-μm thick formalin-fixed and deparaffinized sections with the following markers: CK7, CK20, CDX-2, CEA, PAX-8, WT-1, Vimentin, p53, Estrogen Receptor (ER), p16 and Ki-67.

2.3. Molecular studies

Tumor cells were micro-dissected from unstained slides and tumor DNA was extracted. Mutation analysis of K-ras (codon 12 and 13), BRAF and EGFR (codons 719, 858–861, 768, 790, exon 19del) genes was performed at the Molecular Pathology Laboratory of Indiana University School of Medicine (Indiana, IN), using Applied Biosystems GeneMapper 4.0.
Fig. 1  Histologic examination of the left fallopian tube adenocarcinoma. A) Carcinoma formed a 3 cm intraluminal nodule in the fimbria (40×); B) The tumor predominantly consisted of nodular and confluent glandular growth with cribriform pattern (100×). C) The glandular cells showed eosinophilic or vacuolated cytoplasm and high-grade nuclei. Prominent neutrophils were seen in the lumen and stroma (200×). D) Higher power view of the glands showed marked nuclear atypia with prominent nucleoli and hyperchromasia (400×). Goblet cells were rarely seen in the glands (arrow). E) Goblet cells in the gland-poor areas (400×). F) The tumor eroded fimbria epithelium (200×). G) The tumor replaced fibrovascular stroma in some plicae (200×). H) The tumor invaded into lamina propria, muscle wall and peritubal soft tissue (100×).
Fig. 2  Histologic examination of the metastatic mucinous carcinoma in the left ovary. A, B) Metastatic tumor formed glands and cysts in the ovarian parenchyma (100×). C, D) Cysts and glands were lined by mucinous epithelium (200×). E) The lining epithelium in the cysts was either flat with bland cytology or proliferating with stratification and micropapillary tufts (200×). F, G) Broken glands associated with desmoplasia were present in fibrous septum and residual ovarian parenchyma (100×). Lymphovascular space invasion was exuberant. H) Mucin extravasation was focally seen (100×).
Fig. 3  Histologic examination of the fimbria epithelium uninvolved by carcinoma showing a spectrum of epithelial alteration. A) Flat epithelium with scant cytoplasm, mild nuclear atypia and mitosis (200×). B, C) Stratified epithelium with pale pink cytoplasm, mild nuclear atypia and few goblet cells (200×). D) Stratified epithelium showing positive mucin stain (200×).

Fig. 4  Histology and immunohistochemical stains of mucinous alteration in the fimbria epithelium. A–C) The flat non-atypical mucinous area overlaying the invasive tumor was positive for p53 and negative for ki-67. D–F) The stratified atypical mucinous epithelium was positive for p53 and Ki-67.
3. Results

3.1. Gross and microscopy

Grossly, the left adnexa consisted of a 9 cm ovarian multiloculated cystic mass and a 3 × 2 × 1 cm solid nodule in tubal fimbria. The cyst content had a gelatinous and mucinous consistency. There were also multiple nodular areas in peritubal soft tissue, the largest of which was 1 cm. A 2.5 cm segment of fallopian tube was unremarkable. Also received was a hemorrhagic and friable rectosigmoid mass measuring 4 × 2 × 1 cm in aggregate. Uterus and cervix (9 × 4 × 5 cm) were without lesions. The right ovary (2 × 1.2 × 1 cm) and right fallopian tube (4 cm long and 0.2 cm in diameter) were unremarkable. The omentum was free of nodules. Seventeen pelvic lymph nodes and three para-aortic lymph nodes were retrieved and were without any gross lesions.

Histologic examination of the left fimbria nodule revealed mucinous adenocarcinoma protruding into the lumen (Fig. 1A). The tumor predominantly consisted of glands lined with malignant epithelial cells showing eosinophilic or vacuolated cytoplasm and high-grade nuclei (Fig. 1B–D). Mitoses were abundant. Prominent neutrophils were seen in the lumen and stroma (Fig. 1C). There was no tumor necrosis. Goblet cells were rarely seen in the glands (Fig. 1D) and as single cells in gland-poor areas (Fig. 1E). The tumor eroded fimbria epithelium and replaced fibrovascular stroma in some plicae (Fig. 1F–G). The tumor invaded into lamina propria, muscle wall and peritubal soft tissue (Fig. 1H).

Histologic examination of the left ovarian cystic mass showed mucinous adenocarcinoma in ovarian surface, parenchyma and hilar soft tissue (Fig. 2A–B). The tumor demonstrated a spectrum of morphologic appearances including cysts and glands lined by mucinous epithelium (Fig. 2C–D). The lining epithelium in the cysts was either flat with bland cytology or proliferating with stratification and micropapillary tufts (Fig. 2E). The epithelium in the glands showed mild to severe nuclear atypia. Tumor glands were configured in both heterogeneous lobules and single glands. Disrupted (“broken”) single glands associated with desmoplasia were present in fibrous septum and residual ovarian parenchyma, as were single cells (Fig. 2F–G). Mucin extravasation was focally seen (Fig. 2G–H). Lymphovascular space invasion was exuberant (Fig. 2F). Metastatic carcinoma was also present in the uterine serosa, subserosal myometrium and rectosigmoid region (not shown). The cervix, contralateral adnexa, omentum and all lymph nodes were free of tumor.

Histologic examination of the fimbria epithelium away from, and adjacent to, the carcinoma revealed a spectrum of epithelial changes, from flat atypia with scant cytoplasm (Fig. 3A) to stratified epithelium with abundant pale pink cytoplasm, reminiscent of mucinous alteration (Fig. 3B–C). Mitoses were easily identified in these areas. Few goblet cells were also present in the stratified epithelium, which were highlighted by mucin stain (Fig. 3D).
3.2. Immunohistochemistry

The fimbria carcinoma was strongly positive for CK7 and CEA (Fig. 5A–B), and was completely negative for PAX-8, WT-1, ER, Vimentin, p16, CDX-2 and CK20 (Fig. 5C). P53 stain was weak and variable in about 50% of the tumor cells (Fig. 5D). Ki-67 highlighted more than 90% of the tumor cells (not shown). The flat epithelium in the fimbria was positive for p53 and showed minimal proliferation as assessed by ki-67 (Fig. 4A–C), while stratified atypical epithelium was positive for p53 and Ki-67 (Fig. 4D–F).

3.3. Molecular studies

No mutation in codon 12 and 13 of K-ras gene was detected in the tumor. The BRAF and EGFR genes were similarly wild-type.

4. Discussion

Mucinous adenocarcinoma of the fallopian tube is exceptionally rare, with only 3 cases previously reported in two papers [6,8]. Here we report a moderately differentiated mucinous adenocarcinoma arising in the tubal fimbria in a 70-year-old woman. The tumor had spread to the ipsilateral ovary and other pelvic organs at the time of presentation.

Mucinous lesions, whether benign or malignant, are relatively uncommon in the fallopian tube. The spectrum of mucinous lesions that may be seen at this site is highlighted in the 1997 report of Seidman, wherein 7 mucinous lesions of the fallopian tube were described. The cases included 3 mucinous metaplasias, 2 mucinous cystadenomas, 1 mucinous borderline tumor and 1 carcinoma in situ [14]. That report also affirmed the potential occurrence of a mucinous carcinoma in situ at this location. Morphologically benign mucinous change of the tubal epithelium has been identified as isolated findings, in association with ovarian mucinous tumors, as well as in association with metastases [16,24]. Rare examples of mucinous borderline tumors of putative tubal or paratubal origin have also been described [15,17,18].

Several individual case reports focused on the association of tubal mucinous alterations with the Peutz–Jeghers syndrome, and/or synchronous metaplasia or neoplasm in the other parts of the female genital tract [19–23]. We are aware, however, of only 3 previously reported examples of primary mucinous carcinoma of the fallopian tube diagnosed in the clinical setting [6,8], and these were parts of larger series without comprehensive individual case descriptions.

Since mucinous carcinomas of the adnexa are relatively uncommon, an advanced stage tumor involving the adnexa warrants a careful consideration of the possibility that the tumor is metastatic from elsewhere. In our case, a metastatic carcinoma was excluded based on thorough clinical investigation, which are summarized as the following: 1) multiple imaging studies (both pre-op and post-op) including chest and abdominal CT scans with contrast were all negative for tumors in other organ sites; 2) breast examination and mammogram were negative; and 3) upper endoscopy and colonoscopy were all negative; 4) remote history of cholecystectomy and appendectomy for benign conditions made the appendix and gallbladder unlikely potential sources.

The other options that we considered are the possibility that the ovary, rather than the tube is the primary site, or synchronous primary carcinomas of the ovary and fallopian tube. The latter is very unlikely based on the clinical setting and morphologic features of the tumor. The traditional approach to assigning a primary site to a tumor that involves both the ovary and fallopian tube has been to base the decision primarily on the site of the predominant mass or on size-based criteria for ovarian parenchymal involvement, both of which favored the ovary [25]. However, there is now a robust body of work that implicates the epithelium of the tubal fimbria as the primary site for most adnexal serous carcinomas for both sporadic cancers as well as cancers associated with germline mutations of the BRCA1 or BRCA2 genes [25–32]. These emerging lines of evidence render the traditional approach problematic. However, there have been very limited investigations into the fallopian tube as a potential origin for a subset of adnexal mucinous tumors. In one such study, Shan et al. showed that genetically modified fallopian tube epithelium-derived cell line can generate a poorly differentiated mucinous adenocarcinoma mixed with undifferentiated carcinoma, suggesting that fimbrial epithelial cells of the fallopian tube could be a potential source of ovarian mucinous adenocarcinoma [33]. The pathologic distinction of a primary mucinous of the ovary from a metastatic mucinous tumor to the ovary, is devoid of an absolute gold standard, and is accordingly fraught with some degree of diagnostic irreproducibility.

In a recent study from the Gynecologic Oncology Group, there were unanimity on this point amongst 3 reviewers in only 68% of cases and, disagreement between the reviewers and the original classification in approximately 60% of cases [34]; it can be expected that diagnostic variability would be even higher if the distinction is being made between an ovarian and a tubal origin. Nonetheless, in our case, we rendered the interpretation that the fallopian tube (rather than the ovary sites) is the primary site for the tumor for a variety of reasons: 1) If the Johns Hopkins modification of the laterality and size algorithm is
applied to our case, it will be classified as primary. This algorithm classifies bilateral mucinous carcinomas of the ovary and all unilateral carcinomas <13 cm as metastatic, and reportedly has an 87% accuracy rate in distinguishing primary from metastatic tumors [35]; 2) Our ovarian tumor showed several features that have been associated with metastases, including nodularity, surface involvement, infiltrative invasion, single neoplastic cells, small glands/metastases, including nodularity, surface involvement, showing several features that have been associated with primary from metastatic tumors [35]; 3) Pathologic features of the tumor in the tube included macroscopic and microscopic appearance. Macroscopically, the tumor was located at fimbria and formed a solid nodule protruding into and partially occluding the lumen. Microscopically, the tumor invaded full thickness of the tubal wall into peritubal soft tissue (Fig. 1). The carcinoma partially replaced fimbria plicae and eroded to mucosa epithelium.

The pathologic changes of non-tumorous tubal epithelium were also of interest as possible precursor lesions. These areas showed a spectrum of mucinous alterations with variable nuclear atypia: cytologically bland areas that were reminiscent of mucinous metaplasia were positive for p53 and showed minimal proliferation as assessed by Ki-67, and cytologically atypical stratified mucinous epithelium that was positive for p53 and Ki-67 (Fig. 4). As noted previously, mucinous carcinoma in situ has previously been described [14] and experimental models have shown that in vitro, genetically modified tubal cells can develop tumors with mucinous features [33]. The expression of p53 in a mucinous but otherwise bland tubal epithelium is reminiscent of the “p53 signature”, a latent, non-obligate precursor in the serous model [29] in the serous model. Although p53 signatures are most frequently associated with serous neoplasia of the ovary, they were recently identified in association with 1 of 13 mucinous tumors [37]. The retention of p53 expression in cytologically atypical, proliferative, non-invasive areas of our case suggests progression from the bland p53 signature-like areas, and bolsters the argument that both may be precursors. Where the case differs from the serous model, and which forms an argument against their precursor status, is that the invasive tumor showed a p53 wild type phenotype. These issues warrant further study.

In conclusion, we report a rare case of invasive mucinous adenocarcinoma of probable fallopian tube origin in a 70-year old patient. This is the first comprehensive description of morphologic, immunohistochemical and molecular features of the tumor in English literature.

References

A rare case of invasive mucinous adenocarcinoma of fallopian tube fimbria


